The neural diathesis-stress model of schizophrenia revisited:

An update on recent findings considering illness stage and neurobiological and methodological complexities

Running head: The neural diathesis stress model of schizophrenia revisited

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Abstract

Over the past decade, our understanding of the role of stress in serious mental illness has become more sophisticated. In this paper, we revisit the *neural diathesis-stress model* of schizophrenia that was initially proposed in 1997 and updated in 2008. In light of cumulative research findings, we must now encompass evidence on the premorbid periods of psychosis, and our more nuanced understanding of hypothalamic-pituitary-adrenal (HPA) axis function and its association with neurodevelopmental, epigenetic, neurotransmitter, and inflammatory processes, as well as brain structure and function. Giving consideration to the methodological complexities that have become more apparent as research in this area has burgeoned, the various indices of HPA axis function, and the different stages of illness, we review relevant research published since the 2008 update of the model. We conclude by proposing an extended neural diathesis-stress model that addresses the broader neurobiological context of stress psychobiology in psychosis progression. Implications of this model for best practice, with regards to both future research and treatment strategies, are discussed.

Keywords: stress; psychosis; clinical high risk for psychosis; schizophrenia; neural diathesis stress model; hypothalamus-pituitary-adrenal axis; cortisol, brain; hippocampus; pituitary; stress vulnerability

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List of acronyms:

2-DG - 2-deoxy-D-glucose

ACTH - adrenocorticotropin releasing hormone

AUC - area under the curve

ALT - autoregressive latent trajectory

BDNF - brain-derived neurotrophic factor

CHR - clinical high risk

CAARMS - Comprehensive Assessment of At-Risk Mental States

CRH - corticotrophin releasing hormone

CAR - cortisol awakening response

DST - dexamethasone suppression test

DA - dopamine

ESM - Experience Sampling Method

FEP - first episode of psychosis

fMRI - functional magnetic resonance imaging

GHR - genetic high risk

GWAS - genome-wide association studies

GR - glucocorticoid receptor

HPA - hypothalamic-pituitary-adrenal

IL - interleukin

MR - mineralocorticoid receptor

MIST - Montreal Imaging Stress Task

PET - positron emission tomography

PTSD - post-traumatic stress disorder

SPD - schizotypal personality disorder

SSRI - selective serotonin re-uptake inhibitor

SIPS - Structured Interview for Prodromal Syndromes

SNS - sympathetic nervous system

SAM - sympatho-adrenal medullary system

TSST - Trier Social Stress Test

VBM - voxel-based morphometry

1. Introduction

Stress has long been implicated in the etiology of mental illness, yet it is only within the past two decades that the neurobiological processes mediating this effect have been elucidated by basic and clinical research. In the case of psychotic disorders, which are among the most debilitating mental illnesses, theorists postulated a role for stress in the 1960s (Rosenthal, 1966), but it was not until the 1990's that specific neurobiological mediators were proposed. In 1997, the "neural diathesis stress" model of psychosis was proposed, a model that focused on the role of the hypothalamic-pituitary-adrenal (HPA) axis in triggering and exacerbating psychotic symptoms (Walker and Diforio, 1997). The model was later updated to incorporate subsequent empirical findings that were consistent with its predictions (Walker *et al.*, 2008).

Since the publication of the updated neural diathesis stress model in 2008, research on stress neurobiology, including the role of stress and the HPA axis in mental disorders, has burgeoned. In the present paper, we review the findings from studies of HPA axis abnormalities in diagnosed patients with established and first episode psychosis (FEP), as well as individuals at clinical high risk (CHR) and genetic high risk (GHR) for psychosis, to which the authors of this review have made significant contributions. We consider results obtained with various research designs and methodological approaches, contemplate caveats and challenges in stress research, and take into account the multiple mechanisms that appear to act in concert with the HPA axis in setting the stage for psychosis. We conclude by offering an updated model that considers the complex interplay of vulnerability factors, neurobiological processes and psychosis progression. Finally, we suggest avenues for future research that might help to overcome and understand inconsistencies in this field, and discuss the implications of these findings for treatment options.

1.1 Stress and the HPA Axis

As typically conceptualized by researchers, stress entails a threat to the organism's homeostasis (Frodl and O'Keane, 2013, Hostinar *et al.*, 2014). Broadly defined, the events or 'stressors' that precipitate a sense of threat can be psychological (e g., social rejection) or biological (e g., physical injury or illness). With respect to the former, the nature of the events that are construed as stressors by humans varies among individuals as a function of their personal histories, personality traits, and cognitive appraisals. Thus a relatively benign rebuff by a stranger might be construed as a threat *and* elicit a biological stress response in some individuals, but not others.

Multiple neurobiological systems are activated by stress exposure, and chief among them are the sympatho-adrenal medullary system (SAM) and HPA axis (Joels and Baram, 2009). Both systems govern the release of secretagogues (neurotransmitters, enzymes and hormones) that have the potential to alter brain function. The SAM is activated first and is generally assumed to have more short-term effects when compared to the HPA axis. Further, it is the HPA axis that has received the greatest attention from researchers in the field of psychopathology, and thus it will be the main focus here.

A detailed review of the literature on HPA axis structure and function is beyond the scope of this paper, so the reader is referred to recent overviews that integrate findings from animal and human research (Joels and Baram, 2009, Hostinar *et al.*, 2014). Instead, we describe here the general mechanisms of HPA activity and the impact of its hormonal cascade. Later in this paper we examine in greater detail the association of HPA axis activation with neuronal structure and

function and its role in neuroinflammatory, neurodevelopmental, and epigenetic processes, as well as modulation of dopamine (DA) activity.

The sensory processing of stressful stimuli results in the release of corticotrophin releasing hormone (CRH) from the periventricular nucleus of the hypothalamus. This, in turn, stimulates the anterior pituitary to secrete adrenocorticotropin releasing hormone (ACTH), which then serves to trigger the secretion of glucocorticoids (corticosterone in rodents and cortisol in primates) by the adrenals. Cortisol is the most frequently reported HPA axis measure in research and clinical settings, as it can be easily assayed in blood, urine and saliva. Cortisol assessment in saliva has become the method of choice in the majority of recent studies, as it constitutes a practical and non-invasive tool to reliably measure HPA axis function. Consequently, the focus of our review on HPA axis function will be on cortisol findings.

There are receptors for glucocorticoids throughout the brain, and activation of these serves to provide negative feedback to the hypothalamus to modulate subsequent release of glucocorticoids. Recent evidence from animal research indicates that the negative feedback mechanism involves a complex neurochemical signaling process, such that glucocorticoid receptor activation of hypothalamic neurons following stress serves to dampen the release of CRH via GABA synapses that undergo a change in activity (Inoue *et al.*, 2013). Because the feedback system that keeps HPA activation within normal limits is dependent on the functioning of glucocorticoid receptors, the distribution and sensitivity of these receptors is of critical importance in adaptation to stress.

As a biological system, the HPA axis is essential for survival because it enables the organism to prepare for threatening events and to adjust its behavior to regain homeostasis after stress

exposure. Yet, it is also evident that prolonged activation of the HPA axis, with persistent hypersecretion of glucocorticoids, can have adverse effects on brain structure/function and behavior (McEwen and Gianaros, 2010, Pruessner *et al.*, 2010). These adverse effects involve changes in regional brain volumes as well as changes in neuronal structure and function. Some of the neurobiological pathways leading from stress to brain dysfunction and recent evidence concerning their potential role in psychosis are described in greater detail below.

It is also important to note that there are developmental changes in HPA function. In particular, there are pronounced normative increases in cortisol secretion with the transition into adolescence (Shirtcliff *et al.*, 2012, Holtzman *et al.*, 2013). Further, in healthy subjects, basal cortisol secretion continues to increase with age through adolescence and young adulthood (Walker *et al.*, 2013a). Thus HPA axis function is influenced not only by exogenous stressors, but also by endogenous developmental processes. Moreover, the developmental period associated with normative increases in cortisol secretion is also the period linked with increased risk for onset of mood and psychotic disorders.

1.2 Stress and Psychosis: Initial Evidence Concerning the HPA Axis

Before exploring recent developments in our scientific understanding of the role of the stress and the HPA axis in psychosis, the key research findings that served as the framework for the previous conceptualizations of the neural diathesis-stress model will be summarized (Walker and Diforio, 1997, Walker *et al.*, 2008). The model drew on the accumulated scientific evidence that the HPA axis was activated in response to stress exposure and that its' secretagogues, especially the glucocorticoids, could have widespread effects on brain structure and function.

Glucocorticoids had been shown to alter neuronal functioning and augment the activity of neurotransmitter systems and circuits that had been implicated in the pathophysiology of psychosis. In particular, augmentation of the neurotransmitter DA, which has dominated theorizing about the pathophysiology of psychosis for decades, had been shown to be enhanced by glucocorticoid secretion.

As described by Walker et al. (Walker *et al.*, 2008), there were eight lines of investigation that yielded findings consistent with the model: 1) when compared to healthy controls, indices of basal/baseline HPA activity (cortisol and adrenocorticotropic hormone) are elevated in patients with schizophrenia and other psychoses, especially in non-medicated and first-episode patients; 2) antipsychotic medications typically reduce cortisol, with more pronounced reductions in drug responders; 3) both prescription and recreational drugs that exacerbate or induce psychotic symptoms also increase HPA activity; 4) illnesses (e.g., Cushing syndrome) associated with increased cortisol secretion are also linked with heightened risk for psychotic symptoms/syndromes; 5) receptors for glucocorticoids appear to be down regulated in psychotic patients, suggesting reduced negative feedback on the HPA axis; 6) reduced hippocampal volume, a correlate of hypercortisolemia, is among the most consistently reported brain abnormalities in psychotic patients; 7) in humans, there is a normative increase in baseline cortisol secretion and HPA reactivity during the course of adolescence/young adulthood - the same developmental period when risk for psychosis-onset rises; and 8) the increase in cortisol secretion appears to precede and predict the onset of clinical psychosis in at-risk individuals.

2. Complexities and Caveats in Stress Research

Of course, research with humans, especially clinical populations, often involves confounds that can obscure findings and complicate their interpretation. Before turning to our review of the recent literature on stress and psychosis, several methodological issues that bear on the interpretation of often inconsistent findings should be noted. These include challenges in the measurement of stress and symptoms, the effects of study design, psychotropic medications, sex differences and sociodemographic factors, and differences in cortisol measures and their implications. Although a detailed discussion of these methodological issues is beyond the scope of this paper, it is useful to acknowledge these issues before discussing recent findings, so they can be taken into consideration when drawing inferences based on the research trends.

2.1 The Nature of Stressful Events

A first measurement caveat to note is that conventional self-report measures of life course and everyday stress include events that are assumed to be subjectively stressful to most individuals (e.g., accidents, financial losses, social losses). However, it is clear that subjective experiences of stress are idiosyncratic: events that are deemed stressful by healthy individuals may not be salient to those suffering from or at risk of mental illness. Furthermore, when considering stress in relation to psychotic disorders, our conceptualization must encompass the stress related to preclinical symptoms, the illness itself, perceived stigma, and changes in social relationships and functioning. For example, hallucinations and delusions, as well as the attenuated positive symptoms that emerge in the prodrome, have the potential to trigger stress responses that are not tied to external events (Ward *et al.*, 2014). These stress responses may equal or exceed

those triggered by actual events, yet they would not be indexed by conventional measures of life event or daily stress exposure.

2.2 The associations among different stress measures

A second issue concerns the poor correspondence between various measures of stress. For example, self-reported levels of stress and physiological markers of stress have been shown to be significantly related in only 25% of studies, which could be based on physiological or methodological particularities, or just reflect differences in motivational engagement and social desirability (Campbell and Ehlert, 2012). Furthermore, preexisting levels of chronic life stress and other psychosocial factors can affect biological stress responses (e g., heart rate and blood pressure) to acute stress (Chida and Hamer, 2008), and physiological stress responses of the HPA axis and the SAM might be opposite, actually reflecting compensatory mechanisms (Andrews *et al.*, 2012, Andrews and Pruessner, 2013).

2.3 Limited range in positive symptom severity

A third methodological issue to consider is the limited variance in established symptom domains, which can lead to misleading conclusions when assessing their relationship with stress and biomarkers. For example, the commonly used Structured Interview for Prodromal Syndromes (SIPS) (Woods *et al.*, 2009) and the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung *et al.*, 2005) have upper and lower severity score thresholds for designating risk status. While designation as “prodromal” requires that the individual manifest

a score of 3 to 5 on the six point severity rating scale on at least one of the attenuated positive symptoms on the SIPS, individuals with scores at the lower or upper end of the scale are typically excluded from the sample, because they do not meet criteria for high risk (score 1 or 2), or their symptoms have already reached psychotic severity (score 6). Such exclusion criteria are not applied to ratings of the negative or mood (e g., depression, anxiety) symptoms. As a result, studies using the SIPS and similar measures yield clinical at-risk samples that manifest a restricted range of scores on the positive symptom ratings, but not the other symptom domains. Similarly, by definition, diagnostic criteria for psychotic disorders have no exclusion based on the upper end of the severity distribution of positive symptoms, but in order to meet diagnostic criteria, the lower end must exceed a minimum level of severity. In the context of research, there may also be constraints at the upper end of the continuum of symptom severity in that patients who are acutely psychotic or manifest severe negative symptoms that impede engagement are very unlikely to be recruited to a research study. This will, of course, reduce the likelihood that ratings of positive symptoms will correlate with other measures in both psychotic and CHR samples.

2.4 Cross-Sectional versus Repeated Measures Approaches

Study design is a fourth consideration in the interpretation of data on stress and psychotic syndromes and symptoms. In particular, there are significant limitations to cross-sectional studies in their ability to detect reliable relations of stress measures with symptoms and illness course (Holtzman *et al.*, 2013). With respect to cortisol, the neurobiological effects of circulating glucocorticoids on brain function and behavior are determined by multiple

endogenous factors, most notably glucocorticoid (GR) and mineralocorticoid (MR) receptor distributional patterns, densities and sensitivities. Thus, even if basal cortisol levels were invariant across individuals, the brain and behavioral effects of cortisol will vary among subjects due to receptor characteristics. Individual differences in receptor characteristics will also influence the magnitude of negative feedback on the HPA axis, and, therefore, the cortisol response to stress (Raison and Miller, 2003, van Rossum and Lamberts, 2004). For this reason, studies employing longitudinal, repeated-measures to examine the covariance between biomarkers and symptom severity levels hold the greatest promise for detecting causal relationships. Similarly, there are stable individual differences in the thresholds for reporting both stressful events and the subjective ratings of their stressfulness. A key determinant of the biobehavioral effects of an individual's subjective distress may be the discrepancy between the person's "average" distress and the increase in distress elicited by a particular event. As with biomarkers, the optimal approach to testing the relation of stress with symptom severity is the repeated measurement of both factors over time.

2.5 Psychotropic Medication

Fifth, psychotropic medications can affect baseline HPA hormones. The most common effect is a dampening of HPA activity documented with atypical antipsychotics (Zhang *et al.*, 2005, Cohrs *et al.*, 2006, Venkatasubramanian *et al.*, 2010) and some antidepressants (Manthey *et al.*, 2011). Other antidepressants (Manthey *et al.*, 2011) and stimulant medication (Wang *et al.*, 2012), however, can acutely increase cortisol secretion. Since most diagnosed patients with psychosis are on one or more psychotropics, and many individuals with prodromal

signs/syndromes also have a history of psychopharmacologic treatment (Woods *et al.*, 2013), medication has the potential to obscure differences in HPA indices between clinical and healthy comparison groups. Because atypical antipsychotics and antidepressants usually suppress HPA activity, the result will often be an underestimation of differences between patient and control groups.

Moreover, symptom severity is linked with both the likelihood that medication will be prescribed and the dosage recommended (Woods *et al.*, 2009). Nonetheless, when significant correlations are observed between baseline cortisol and symptom severity, they are consistently positive in both psychotic (Belvederi Murri *et al.*, 2012) and CHR patients (Walker *et al.*, 2013b). Thus, it is plausible that those with the greatest pretreatment elevations in HPA activity are the most likely to be medicated. If prodromal symptom severity is even modestly linked with HPA activity prior to medication, then the medicated patients may have experienced a medication-induced dampening of HPA activity prior to baseline assessment. Again, the consequence will be an underestimation of group differences in HPA indices.

2.6 Sex differences and Interactions

A sixth caveat to be considered is the presence of sex differences. Male compared to female patients have higher rates of treated incidence of psychosis (Aleman *et al.*, 2003, Anderson *et al.*, 2012), show an earlier age of onset (Hafner *et al.*, 1998, Cascio *et al.*, 2012), exhibit more negative symptoms (Morgan *et al.*, 2008, Chang *et al.*, 2011), experience greater functional and social impairment (Scott, 2011), and are treated with higher doses of antipsychotic medication (Smith, 2010). Some of the sex differences that characterize psychotic patients have also been

observed in CHR patients (Walder *et al.*, 2013, Barajas *et al.*, 2015), including greater social role functioning impairments and (prodromal) symptom severity in male compared to female patients. In fact, poorer baseline social functioning and greater positive symptoms predicted higher conversion rates in male but not female patients (Walder *et al.*, 2013).

Sex differences have also been reported for various indices of HPA axis function in both animal and human studies (for reviews see, (Kirschbaum *et al.*, 1999, Kudielka and Kirschbaum, 2005, Goel *et al.*, 2014). In rodents, both basal and corticosterone secretion in response to physical and psychological stressors are consistently reported to be higher in females compared to males (Goel *et al.*, 2014). In humans, the picture is less conclusive. Basal cortisol levels (Paris *et al.*, 2010) and cortisol increases in response to the TSST (Kudielka and Kirschbaum, 2005) appear to be higher in men compared to women, whereas studies employing pharmacological stimulation of the HPA axis, physical stressors or tasks involving social rejection, tend to elicit greater cortisol responses in women (Goel *et al.*, 2014). Studies on the cortisol awakening response (CAR) demonstrate a comparable cortisol increase in healthy men and women, but a delayed decrease to baseline levels in women (Pruessner *et al.*, 1997a, Wust *et al.*, 2000). However, a recent population-based study found no sex difference in the CAR in adolescents (Bouma *et al.*, 2009). Based on these findings, the consideration of sex differences has the potential to explain inconclusive findings related to group differences between patients and healthy controls and related to associations between symptoms and stress markers.

2.7 Sociodemographic factors

A final caveat to consider when evaluating the relationship between psychosis and HPA axis function relates to the potentially confounding effects of sociodemographic factors. Ethnic differences in schizophrenia/psychosis rates have been the source of much investigation in the UK with pooled data indicating that the risk of schizophrenia is approximately 4-5 fold higher among black Caribbean and black African groups relative to the white British population (Kirkbride *et al.*, 2012). Although less frequently investigated, rates of schizophrenia have been found to be similarly elevated among African American individuals relative to Caucasian persons in the US (Bresnahan *et al.*, 2007). There is additionally evidence of socioeconomic differences in schizophrenia/psychosis *risk*. Specifically, increased risk of schizophrenia has been associated with both low socioeconomic status in childhood (Wicks *et al.*, 2005, Corcoran *et al.*, 2009) and residing in neighborhoods of increased deprivation in adulthood (Kirkbride *et al.*, 2014).

While the mechanisms underlying the relationship of schizophrenia and other psychoses with ethnic minority and lower socioeconomic status are unclear, importantly, both sociodemographic factors have also been associated with HPA axis function. Studies in the US have reported that relative to Caucasian individuals, those of black ethnicity are characterized by higher baseline cortisol levels in the evening (Cohen *et al.*, 2006, Fuller-Rowell *et al.*, 2012) lower cortisol levels upon awakening (DeSantis *et al.*, 2007, Fuller-Rowell *et al.*, 2012), and a more blunted cortisol response during psychosocial stressor tasks (Chong *et al.*, 2008). Additionally, studies of both children (Lupien *et al.*, 2001) and adults (Cohen *et al.*, 2006) have observed elevated baseline cortisol levels among individuals of low socioeconomic status compared to individuals from high socioeconomic backgrounds. A large study of adolescents

further reported a U-shaped association between socioeconomic status and CAR, such that adolescents from high and low socioeconomic families showed a blunted CAR relative to adolescents from intermediate families (Marsman *et al.*, 2012). Thus, ethnicity and socioeconomic status should be considered as important factors that may confound, mediate, or modify the relationship between HPA axis function and psychosis.

2.8. The measurement of baseline cortisol and cortisol change

2.8.1 Baseline cortisol measures:

The term 'baseline' has typically been used to refer to the initial measurement of a variable in the absence of any experimental manipulation or exposure (Rogosa, 1995). 'Baseline' cortisol levels can be estimated by obtaining a single fluid sample (saliva, urine, or blood). Because cortisol exhibits a distinct circadian rhythm (levels are highest in the morning, gradually decline throughout the day, and rise again during sleep), controlling for sampling time is important when employing single cortisol samples as baseline measures. To overcome this problem, some studies have obtained multiple samples throughout the day to examine diurnal patterns of secretion. These multiple measures can then be analyzed using repeated measures statistics or calculating the area under the curve (AUC) (Pruessner *et al.*, 2003a), yielding a single value that is informative of baseline HPA axis function. A relatively novel method to retrospectively assess HPA axis activity over extended periods of time is hair cortisol (Beasley *et al.*, 2000, Russell *et al.*, 2012, Stalder and Kirschbaum, 2012, Staufenbiel *et al.*, 2013). This method measures systemic cortisol exposure on a month by month basis, and can provide

useful complementary information to the real time cortisol measures captured with other methods.

2.8.2 Cortisol levels in response to stimulation

Repeated cortisol sampling has also been used to examine changes following exposure to (i) experimentally-induced stress, (ii) naturally occurring stressors, or (iii) pharmacological challenge. Changes in HPA axis activity in response to acute stress are typically elicited with psychosocial stressor tasks and usually involve assessing cortisol levels before, during, and after the task.

2.8.2.1 The Cortisol Awakening Response (CAR)

The cortisol awakening response (CAR) refers to the sharp increase in cortisol that typically occurs within 15-40 minutes of waking (Pruessner *et al.*, 1997b). The CAR seems to be distinct from – and superimposed on — the diurnal cortisol course, and is thought to be triggered by the sleep-wake transition and the associated anticipation of the upcoming day (Wilhelm *et al.*, 2007, Fries *et al.*, 2009). It is conceivable that cortisol measures taken in close proximity to the time of awakening are influenced by the awakening process rather than reflecting 'baseline' cortisol secretion. Due to challenges with reliably measuring the CAR, especially outside of the laboratory, investigators in the area have recently proposed guidelines for obtaining measures of the CAR and analyzing CAR data (Stalder *et al.*, 2016).

2.8.2.2 The Trier Social Stress Test

The Trier Social Stress Test (TSST) is an established laboratory protocol to evaluate cortisol and other physiological responses to a moderate psychosocial stressor, typically consisting of a job interview and mental arithmetic (5 minutes each) in front of an audience and a camera (Kirschbaum et al., 1993). The task aims to induce social evaluative threat and uncontrollability, two important characteristics of psychological stressors to evoke strong cortisol responses in target individuals (Dickerson and Kemeny, 2004). In order to minimize the impact of diurnal rhythm on the cortisol responses, all participants should be seen at the same time of day, ideally in the afternoon.

2.8.2.3 The Montreal Imaging Stress Task (MIST)

Designed to induce stress in a functional neuroimaging environment, the Montreal Imaging Stress Task (MIST) presents mental arithmetic tasks on a computer screen during the scanning procedure. Experimental and baseline conditions differ in task difficulty as well as visual and verbal feedback by the experimenter. In addition, task difficulty in the experimental condition is constantly adjusted by the computer to be just beyond the participant's highest performance level (Dedovic *et al.*, 2005).

2.8.2.4 The Experience Sampling Method

Responses to naturally occurring stressors have been examined using the Experience Sampling Method (ESM), a structured diary technique (Myin-Germeys and van Os, 2007). Briefly,

participants are prompted by a digital wristwatch at random intervals throughout the day and asked to describe stressful experiences, provide ratings of current mood and symptoms, and collect a salivary cortisol sample.

2.8.2.5 Pharmacological cortisol challenges

Finally, changes in HPA axis function can be assessed following administration of a pharmacological agent. The most commonly utilized method is the dexamethasone suppression test (DST), which involves administering dexamethasone (a synthetic glucocorticoid) in order to determine whether the HPA axis negative feedback system is effective in suppressing cortisol secretion. Another laboratory procedure involves administering 2-deoxy-D-glucose (2-DG), a glucose analogue that blocks glycolysis and induces cortisol secretion.

2.8.3 Statistical complexities

There are a number of statistical complexities associated with the measurement of change in bio-behavioral variables, including cortisol (Rogosa, 1995, Burt and Obradović, 2013, Chiolero *et al.*, 2013). According to the 'law of initial values', the magnitude of stress induced change in cortisol can be inversely related with the baseline or 'initial' cortisol level (Balodis *et al.*, 2010, Miller *et al.*, 2013). As a consequence, individuals characterized by chronically elevated cortisol secretion may not show an increased experimental stress-induced cortisol response. To address this problem, Miller and colleagues (Miller *et al.*, 2013) recommend alternative

statistical approaches to indexing cortisol responsivity, including, autoregressive latent trajectory (ALT) mixture models and baseline-adjusted log-transformed criteria that reduce false-negative classification of subjects as non-responders. However, these approaches have not yet been applied to data from stress-induction paradigms with psychotic, CHR or GHR samples.

2.8.4 The impact of confounding factors

Both hyper- and hypo-activation of the HPA axis have been associated with similar pathological outcomes (Heim *et al.*, 2000a, Fries *et al.*, 2005, Miller *et al.*, 2007). Similarly, repeated measures over days or weeks with the same method do not guarantee identical results. These discrepancies in HPA axis activation may be a function of habituation, personality, situational factors (Pruessner *et al.*, 1997a) or increasing age (Lupien *et al.*, 1994); Holtzman et al., 2013; (Platje *et al.*, 2013). Finally, given the novelty and potential stressfulness of research participation, baseline cortisol levels observed in the laboratory may be elevated compared to the level that would have occurred in a natural environment. It is not clear, therefore, that a 'true' baseline stress measure can be obtained in the laboratory.

2.8.5 Summary

In summary, researchers should be aware that, on the one hand, cortisol levels obtained with varying methods, at different times of the day, in the form of single or repeated measures, at baseline or in response to stimulation, are likely to entail different mechanisms and yield

different results (Buchanan *et al.*, 2004, Wolf *et al.*, 2005, Buchanan *et al.*, 2009). On the other hand, awareness and control of subjective, situational and methodological confounds is essential to achieve valid and reproducible results.

3. Research Update on HPA Axis Function among those with Psychosis and At-Risk for Psychosis

As noted in previous reviews (Walker and Diforio, 1997, Walker *et al.*, 2008), research has provided ample evidence of cortisol abnormalities among individuals with established psychosis. However, in accordance with the clinical staging model of psychosis, it has been proposed that subtle neurobiological abnormalities should be detectable in early illness phases and evolve as the illness progresses, thereby constituting potential predictors of transition to psychosis (McGorry, 2013). This has sparked an interest in the investigation of HPA axis function prior to illness onset among individuals at putative prodromal phases or at elevated risk for the disorder.

In the past, the identification of at-risk individuals focused primarily on those at putative GHR due to a family history of illness. Given the limited generalizability of this approach (i.e., the majority of individuals with schizophrenia do not have a first-degree relative with the disorder and the majority (>80%) of biological offspring of patients do not develop psychosis) (Lichtenstein *et al.*, 2009), other strategies focusing on clinical presentation have emerged. The most widely-implemented of these is the CHR approach, examining help-seeking adolescents and young adults who display symptoms consistent with the prodromal phase of illness, that typically precedes the onset of florid psychosis and is characterized by attenuated psychotic

symptoms, as measured by standardized diagnostic interviews and criteria (Woods *et al.*, 2009, Fusar-Poli *et al.*, 2013). Risk rates for subsequent psychosis in those who meet CHR criteria range between 20 and 40% over two years (Addington and Heinssen, 2012, Fusar-Poli *et al.*, 2012a), but can be even lower (Pruessner *et al.*, 2015a).

Researchers have also studied non-help-seeking samples who report subclinical psychotic symptoms which, although not uncommon, confer elevated risk for psychosis (Kaymaz *et al.*, 2012). Other studies focus on individuals who are at elevated risk for psychosis because they meet diagnostic criteria for schizotypal personality disorder (SPD), a disorder assumed to be on the schizophrenia spectrum because it is more often present in the biological relatives of schizophrenia probands.

In the following sections, we review the results of studies published since our 2008 review, examining three indices of HPA axis function among psychotic patients and those at risk for psychosis: (i) baseline cortisol, (ii) the cortisol awakening response, and (iii) cortisol responses to stress and pharmacologic challenge. The results suggest that these measures index different aspects of the stress response and have partially independent determinants.

3.1 Baseline Cortisol

Recent studies of baseline cortisol levels in psychosis generally yielded results consistent with our previous review (Walker *et al.*, 2008), showing elevated cortisol levels in patients with established psychosis relative to healthy controls in blood (Venkatasubramanian *et al.*, 2010, Yildirim *et al.*, 2011, Girshkin *et al.*, 2014). Similarly, recent systematic reviews and subsequent studies also indicate that plasma/serum cortisol levels are elevated among individuals

experiencing their first episode of psychosis (FEP) (Borges *et al.*, 2013, Karanikas *et al.*, 2014, Carol and Mittal, 2015, Dogan Bulut *et al.*, 2016). However, not all studies have replicated these findings, particularly when medication effects were not controlled for (Strous *et al.*, 2004, Garner *et al.*, 2011, Garcia-Rizo *et al.*, 2012, van Venrooij *et al.*, 2012). Such medication effects on baseline cortisol levels become most evident when reviewing the literature on studies measuring cortisol in saliva. Here, higher diurnal cortisol levels relative to controls were observed only among antipsychotic-naïve or minimally-treated first-episode psychosis patients (Gunduz-Bruce *et al.*, 2007, Mondelli *et al.*, 2010a). In contrast, studies of first-episode patients, the majority of whom were treated with antipsychotic medication, did not observe elevated diurnal cortisol AUC (Hempel *et al.*, 2010). Indeed, the medicated patients were found to show a sharper decrease in cortisol levels throughout the day (Hempel *et al.*, 2010). Accumulated evidence thus indicates that cortisol levels during the day are elevated among individuals with psychosis and that inconsistent findings across studies may reflect the dampening effects of antipsychotic medication.

Elevated baseline cortisol levels in both blood and saliva have similarly been observed among individuals at risk for psychosis, although the consistency of this finding varies (Aiello *et al.*, 2012, Carol and Mittal, 2015, Karanikas and Garyfallos, 2015). Two recent studies reported higher cortisol levels in a single salivary sample among CHR youth relative to controls (Sugranyes *et al.*, 2012, Carol and Mittal, 2015). Again, this group difference was more pronounced among those who were medication-free (Sugranyes *et al.*, 2012). Similarly, studies examining salivary cortisol at multiple time-points throughout the day have observed elevated levels among youth at CHR for psychosis (Walker *et al.*, 2013b), adolescents with SPD

(Weinstein *et al.*, 1999, Walker *et al.*, 2001, Mittal *et al.*, 2007), and young adults with high scores on a measure of subclinical psychotic symptoms (Mittal *et al.*, 2013).

In contrast, a study examining fasting morning levels of both salivary and plasma cortisol obtained at a single time-point in a laboratory setting reported that CHR youth did not differ significantly from healthy controls on either measure (Labad *et al.*, 2015). Similarly, two recent studies, which implemented a home saliva sampling protocol, failed to observe increased diurnal cortisol among CHR youth (Day *et al.*, 2014) or children with either a family history of illness or multiple antecedents of schizophrenia (Cullen *et al.*, 2014b). It is possible that the uncontrolled in-home environment and extended sampling period might increase error variance and inter-individual variation in cortisol measurement, which would diminish power to detect group differences.

It appears that findings furthermore differ between studies with GHR and CHR groups. Two studies of individuals with a family history of illness, one examining serum cortisol in a non-fasting blood sample (Yildirim *et al.*, 2011), and the other in multiple salivary cortisol samples obtained throughout the day (Collip *et al.*, 2011) both showed elevated cortisol levels in relatives compared to controls. However, four studies utilizing fasting plasma cortisol samples did not (Marcelis *et al.*, 2004, Spelman *et al.*, 2007, Brunelin *et al.*, 2008, Yang *et al.*, 2012). Indeed, lower cortisol levels (albeit non-significantly lower) were observed among relatives in three of these studies. As noted above, however, most with a family history of psychosis do not go on to develop a psychotic disorder. Thus the majority of GHR subjects will be false positives. In contrast, the rate of conversion to psychosis is higher in CHR samples and they are, by definition, characterized by the presence of a clinical syndrome.

A recent study directly compared salivary cortisol levels in samples collected at a single time-point (09:00 am) in FEP patients, individuals at CHR, and help-seeking individuals who did not meet CHR criteria (Chaumette *et al.*, 2016). Interestingly, cortisol levels were not significantly different across the three groups, even after adjusting for a range of potential confounders (including medication use). A problem with most cortisol measures at a fixed time point in the morning is that they may have been confounded by the cortisol awakening response. However, it cannot be excluded that elevations in basal cortisol reflect general distress associated with mental health problems rather than psychosis risk per se.

Longitudinal studies of at-risk youth have also yielded somewhat inconsistent findings. A study of at-risk youth who were assessed at baseline and at 7- and 12-month follow-ups, showed that cortisol levels at baseline did not differ between converters and non-converters, but that converters showed higher cortisol levels at follow-up assessments (Walker *et al.*, 2010). However, a subsequent study examining a larger sample of CHR youth indicated that cortisol levels at study onset were significantly elevated among those who transitioned to psychosis within two years relative to healthy controls and CHR youth whose symptoms had remitted (Walker *et al.*, 2013b). In contrast, a recent study of CHR subjects failed to show an association between transition to psychosis and cortisol levels measured at the time of recruitment, however some were on antipsychotics (Chaumette *et al.*, 2016). Two recent studies employing hair cortisol showed that elevations in basal HPA axis activity precede the onset of psychosis (Andrade *et al.*, 2016) and mark an acute illness course as opposed to remission (Streit *et al.*, 2016).

3.2 Cortisol Awakening Response

Recently, the focus of research related to HPA axis function in psychosis has shifted to the investigation of the cortisol awakening response (CAR), but the number of studies is limited. Again, findings here are somewhat inconsistent, and the influence of confounding factors is likely. The most influential study in this area to date reported a blunted CAR among first-episode patients relative to controls (Mondelli *et al.*, 2010a). In contrast, several other studies did not observe a significant group difference in the CAR in FEP patients (Pruessner *et al.*, 2008, Hempel *et al.*, 2010, Pruessner *et al.*, 2013b, Girshkin *et al.*, 2016) and in patients with established psychosis (Monteleone *et al.*, 2015) compared to healthy controls. A series of studies by the first author suggests that any indication of such group differences is driven by confounding factors such as sex differences and the time of awakening (Pruessner *et al.*, 2008, Pruessner *et al.*, 2013b, Pruessner *et al.*, 2015b). In line with this notion, other studies suggest that a blunted CAR might be associated with factors such as a poor response to antipsychotic medication (Mondelli *et al.*, 2015), cannabis use (Monteleone *et al.*, 2014) or simply poor sampling adherence (Berger *et al.*, 2016).

Few studies have examined the CAR in at-risk individuals. Two studies observed a blunted CAR compared to controls, one among CHR youth (Day *et al.*, 2014), and another in children aged 11-14 years (Cullen *et al.*, 2014b). In contrast, a blunted CAR was not observed among children at-risk due to the presence of multiple antecedents of schizophrenia (Cullen *et al.*, 2014b) and in another recent study in CHR individuals (Pruessner *et al.*, 2016). However, in line with our

findings in FEP patients, male patients showed a trend for blunted cortisol levels following awakening compared to female patients (Pruessner *et al.*, 2016). Similarly, another recent study found no difference in cortisol levels over two hours after awakening between CHR individuals and controls, but observed a significantly blunted cortisol response in male compared to female patients (Carol *et al.*, 2016). Yet another recent study observed an *increased* CAR in at-risk youth who transitioned to psychosis within one year relative to both CHR youth who did not transition and healthy controls (Labad *et al.*, 2015). Considering the conflicting evidence, a recent systematic review and meta-analysis on the CAR in patients at different stages of the psychosis continuum comes to the conclusion that the CAR is attenuated in patients with established psychosis, but not in individuals at CHR (Berger *et al.*, 2016). As acknowledged by the authors themselves, the number of studies on the CAR in this area is limited, and factors such as comorbidities, adherence and response to medication, and adherence to sampling procedures will need to be controlled for in future studies (Berger *et al.*, 2016).

3.3 Cortisol Responses to Stress and Pharmacologic Challenge

Studies investigating the cortisol response to acute challenges across the psychosis spectrum are also few in number. Confirming previous reports (Jansen *et al.*, 1998, Jansen *et al.*, 2000), recent studies have reported a blunted cortisol response to a public speaking task in patients with chronic schizophrenia (Brenner *et al.*, 2009) and in medication-naïve FEP patients (van Venrooij *et al.*, 2012) relative to healthy controls. Despite the similar findings in medicated and non-medicated patients, antipsychotic use appears to contribute to a blunted cortisol response

to stress (Houtepen *et al.*, 2015). Similar to findings in established psychosis, the cortisol response to the TSST has also been shown to be blunted among antipsychotic-naïve CHR youth relative to controls (Pruessner *et al.*, 2013a). In contrast, a study using a mental arithmetic task during a positron-emission tomography (PET) scan, found a decrease in salivary cortisol during the task in controls and no change in CHR youth (Mizrahi *et al.*, 2012). In an earlier study using this stress paradigm during a PET scan, both youth with schizotypal traits and healthy controls showed a significant cortisol response, with no significant difference between the groups (Soliman *et al.*, 2008). The cortisol response in these latter studies might have been confounded by the potentially stress-inducing environment of a PET scan. Furthermore, small subject numbers in these studies indicate the need for further validation of the results.

Using the experience sampling method (ESM), a study of an adult GHR sample observed an increase in the cortisol response to unpleasant events, that was not present among healthy controls (Collip *et al.*, 2011). However, in a subsequent report based on a subsample from this study, the cortisol response to daily stressors in both patients and their siblings did not differ from that of healthy controls (Habets *et al.*, 2012), which may reflect a lack of statistical power due to the smaller sample size.

Early studies employing the Dexamethasone suppression test (DST) had reported that patients with schizophrenia (the majority of whom were receiving antipsychotic medication) were more likely to be classified as dexamethasone 'non-suppressors' than controls (Banki *et al.*, 1985, Baumgartner *et al.*, 1986, Lammers *et al.*, 1995). Recently, higher post-dexamethasone cortisol levels and higher rates of dexamethasone non-suppression relative to controls have also been reported in studies of patients with psychotic depression (Schatzberg, 2015). In contrast, the

only study comparing first-episode psychosis patients to controls reported higher rates of cortisol hyper-suppression in patients (Phassouliotis *et al.*, 2013). A small sample (n=12) study by this group also reported that, contrary to hypotheses, antipsychotic-naive CHR youth who later transitioned to psychosis (n=3) had lower post-dexamethasone cortisol levels than those who did not (Thompson *et al.*, 2007a). While these two reports of increased cortisol hyper-suppression are similar to findings observed in patients with PTSD, and may therefore indicate enhanced inhibition of cortisol via negative feedback (Yehuda, 2001, 2002), they should be interpreted with caution due to the small sample sizes and the fact that some subjects were on antipsychotic medication. Results of the 2-deoxy-D-glucose (2-DG) test on cortisol levels have been inconclusive (Elman *et al.*, 1998, Marcelis *et al.*, 2004, Mitropoulou *et al.*, 2004, Brunelin *et al.*, 2008), and recent findings are lacking. Incongruent findings likely reflect differences in methodology and sample characteristics.

3.4 Specificity of HPA axis abnormalities to psychosis

Abnormal cortisol levels have also been observed among other psychiatric disorders, most notably, depression and post-traumatic stress disorder (PTSD). Recent meta-analyses indicate that individuals with depression are characterized by elevated diurnal cortisol levels (Stetler and Miller, 2011), a blunted cortisol response to stress and impaired stress recovery compared to non-depressed controls (Burke *et al.*, 2005). Further, research has shown that depressed patients with psychosis have higher cortisol levels than nonpsychotic depressed patients and healthy controls (Keller *et al.*, 2016). Whilst the CAR has been less frequently examined in this population, several studies have observed an increased CAR among both adolescents and

adults with depression (Bhagwagar *et al.*, 2003, Dienes *et al.*, 2013, Ulrike *et al.*, 2013) and individuals with subclinical depression symptoms (Pruessner *et al.*, 2003b) relative to healthy controls. In contrast, there is evidence that individuals with PTSD, like those with psychosis, are characterized by a blunted CAR (Chida and Steptoe, 2009). However, *decreased* cortisol levels during the day have been consistently reported among PTSD patients relative to controls (Morris *et al.*, 2012). Yet another picture emerges in panic disorder patients, who show little or no alteration in basal cortisol levels and a normal CAR, but a distinctive non-responsiveness to a psychosocial stressor (Petrowski *et al.*, 2010). Thus, the pattern of cortisol abnormalities observed among individuals with psychosis shares some features with other disorders, yet the elevated diurnal cortisol levels in combination with a blunted CAR appear to reflect a specific profile that is distinct from that observed in depressed and PTSD populations (Borges *et al.*, 2013).

3.5 Sex differences in HPA axis function in psychosis

As described in section 2.6, there are well-documented sex differences in the course of schizophrenia and other psychotic disorders. There are also some normative sex differences in HPA function and cortisol secretion (Paris et al., 2010). In the context of various health and psychopathological conditions, both elevated and blunted CARs have been reported (Kudielka and Wust, 2010). Interestingly, low grade depressive symptomatology in non-clinical samples has been associated with an elevated CAR in males (Pruessner *et al.*, 2003b) and a blunted CAR in females (Stetler and Miller, 2005), suggesting that the consideration of sex differences might help to explain inconsistent findings.

In patients with psychosis (Girshkin *et al.*, 2014) and CHR samples (Walker et al., 2013) no sex differences have been reported for baseline cortisol measures; however, sex differences might become evident when the HPA axis is stimulated (by awakening or psychological/mental challenges). Indeed, Pruessner et al. recently observed a blunted CAR in male patients compared to female FEP patients (Pruessner *et al.*, 2008, Pruessner *et al.*, 2013b, Pruessner *et al.*, 2015b) and compared to male healthy controls (Pruessner *et al.*, 2015b). Similarly, a recent study in individuals at CHR found a trend for a smaller CAR in male compared to female patients (Pruessner *et al.*, 2016), and a study measuring cortisol over three time points in the morning observed flat cortisol levels in male compared to female CHR subjects (Carol *et al.*, 2016). In these studies, no significant sex differences in the CAR were observed in the control group, or when female patients were compared with same-sex controls. Our research furthermore demonstrated an association between attenuated cortisol levels post awakening and smaller hippocampal volume, again predominantly in male patients (Pruessner *et al.*, 2015b). Interestingly, sex differences in the CAR were not reported in other recent studies including FEP patients (Mondelli *et al.*, 2010a), individuals at CHR (Day *et al.*, 2014) and children at familial high risk for psychosis (Cullen *et al.*, 2014b).

With respect to mental challenge tasks, Brenner and colleagues reported higher cortisol levels (both prior to and during the task) in male relative to female participants across both patients with established psychosis and controls (Brenner *et al.*, 2009). These authors had observed a blunted cortisol response to stress in the total patient group compared to controls (described above), suggesting that alterations in HPA axis function related to pathologic processes are superimposed on existing sex differences. However, two other recent studies investigating the cortisol response to mental challenge did not find sex differences in FEP (Mizrahi *et al.*, 2012)

and CHR patients (Pruessner *et al.*, 2013a). Possible determinants of the scarcity of sex differences related to HPA axis function in psychosis might be the generally small number of participants and relatively smaller number of female than male patients in these studies, often resulting in a lack of statistical power in sex specific analyses. Further, there is evidence that stress-induced cortisol levels in women vary with menstrual cycle phase (Kudielka and Kirschbaum, 2005, Walder *et al.*, 2012), impeding the chances to find significant sex differences when this factor is not controlled. Clearly, further investigation of sex differences with respect to HPA axis function in psychosis and high-risk populations is warranted.

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Insert Table 1

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3.6 Summary

Table 1 provides a summary of reported cortisol abnormalities among those with established psychosis and those at-risk for the disorder. As illustrated, there is evidence that patients with chronic schizophrenia and first-episode psychosis are characterized by elevated baseline cortisol levels, but that this finding is less consistent among patients treated with antipsychotic medication. Baseline cortisol elevations have similarly been reported among youth at CHR for psychosis and adolescents with SPD; however, findings among GHR individuals and children presenting multiple antecedents of schizophrenia have been inconsistent. This is perhaps to be

expected, given that the rate of conversion to psychosis is much lower in GHR subjects when compared to CHR subjects (Woods *et al.*, 2009). Thus, GHR samples are less 'enriched' in that they include a smaller proportion of individuals who will subsequently be diagnosed with a psychotic disorder.

Findings relating to the CAR are mixed. While several studies have observed a blunted CAR among patients with psychosis and individuals at CHR for the disorder, relative to healthy controls, other studies have observed no group differences or found an *increased* CAR in individuals at CHR compared to controls. A recent systematic review and meta-analysis on the subject comes to the conclusion that the CAR is attenuated in established and first episode psychosis, but not in individuals at CHR (Berger *et al.*, 2016).

As yet, there is little evidence of heightened HPA responsivity from experimental studies using stress or pharmacologic challenge. Generally, patients with psychosis appear to show a blunted cortisol response during psychosocial stressor tasks and increased rates of cortisol 'non-suppression' to the DST. These trends have not been consistently replicated in at-risk samples. Studies administering 2-DG have likewise generated contrasting findings. As described in section 2.8.3, however, measurement of HPA responsivity to challenge is complicated by individual differences in baseline levels. To date, studies of responsivity in psychotic and high-risk samples have not employed the statistical approaches that appear optimal for addressing this problem (Miller et al., 2013). In sum, research findings to date have provided fairly consistent evidence that elevated baseline cortisol levels characterize both psychosis patients and CHR individuals, but studies of the CAR and HPA axis responses have been somewhat inconsistent. Conflicting findings in both groups might be explained by the use of medication or

methodological differences such as measurement time (morning, diurnal), measurement frequency and pattern (e.g. single, repeated), location (home, laboratory), sampling method (saliva, blood), sampling adherence, or group characteristics (family history of psychosis, illness stage, sex differences). Further studies using more stringent methodological and statistical approaches are needed.

4. Stress, Cortisol, and Symptoms

4.1 Stress exposure, perceived stress and early life adversity

There is now substantial evidence to support the notion that psychosocial stress contributes to the onset and exacerbation of psychotic symptoms in vulnerable individuals. An early study demonstrated that both major life events and subjective experiences of stress predicted poor clinical outcome among patients with established schizophrenia, although perceived stress showed a more reliable relationship to symptomatology than major life events (Malla and Norman, 1992). This has been supported by numerous subsequent studies (Holtzman *et al.*, 2013). Similarly, CHR patients who later converted to psychosis reported a greater number of life events, and perceived these events as more stressful, compared to healthy controls and CHR subjects whose symptoms remitted (Trotman *et al.*, 2014). Perceived stress levels in CHR patients are generally high (Moskow *et al.*, 2016), and in some studies they even exceed ratings in FEP patients (Pruessner *et al.*, 2011, Palmier-Claus *et al.*, 2012).

Recent research has also demonstrated a relationship of higher perceived stress with depression and positive symptoms in both at-risk samples (Pruessner *et al.*, 2011, Tessner *et al.*, 2011, Palmier-Claus *et al.*, 2012, Devylder *et al.*, 2013, Cullen *et al.*, 2014a) and first episode psychosis patients (Raune *et al.*, 2006, Lataster *et al.*, 2013). However, as noted above, elevated stress levels may be secondary to illness related factors, rather than causal. Similarly, at the neural level, while there has been an emphasis on the role of cortisol in the expression of symptoms through effects on dopaminergic pathways ("bottom-up" model), it is also possible that symptoms and corresponding neurotransmitter activity affect HPA axis activity ("top down" model) (Belvederi Murri et al., 2012).

It has been suggested that especially earlier and/or longer term, rather than acute or recent perceived stress affects pathophysiological processes in psychosis (Alameda *et al.*, 2015, Nugent *et al.*, 2015). Here, a well-documented risk factor for psychosis is early life adversity (Gibson *et al.*, 2016). A large-scale meta-analysis including 45,441 individuals concluded that childhood trauma is strongly linked to increased risk of developing a psychotic disorder, with an overall effect of OR=2.78 (95% CI=2.34-3.31) (Varese *et al.*, 2012). This association was still significant after adjustment for genetic risk, supporting the notion of a causal relation between early life adversity and psychosis (van Winkel *et al.*, 2013). A recent study of CHR individuals showed that a history of childhood sexual abuse increased the transition rate to psychosis up to 2-4 times (Thompson *et al.*, 2014). Other research suggests that childhood trauma particularly affects positive and dysthymia symptoms (Ruby *et al.*, 2015) and that patients who have experienced childhood trauma show delayed symptom remission (Aas *et al.*, 2016). Of course, the adverse effects of childhood trauma are not specific to psychosis, and victims of childhood trauma show a range of symptoms and syndromes (van Nierop *et al.*, 2014, Gibson *et al.*, 2016).

Early life stress in particular appears to have enduring effects on the brain and stress regulatory systems, including the autonomic, endocrine and immune systems, which may lead to a lifelong increased vulnerability to subsequent stress and consequences for detrimental long-term health outcomes (Heim and Binder, 2012). Both animal (Liu *et al.*, 1997, Anisman *et al.*, 1998) and human (Devylder *et al.*, 2013, Trotman *et al.*, 2014) studies have shown that previous exposure to stressful events can lead to stress-sensitization and dysregulation of the HPA response when confronted with subsequent stressors, both of which are believed to be critical contributors to the development of psychosis. Trauma victims not only responded with more subjective distress to stressful experiences later in life (Veling *et al.*, 2016), the experience of early life adversity also predicted attenuated cortisol responses to a public speaking task in a dose-dependent fashion (Lovallo *et al.*, 2012). Similarly, a study of FEP patients recently showed an association between poor parental bonding, an indicator for early life adversity, and a blunted cortisol awakening response (Pruessner *et al.*, 2013b). Some studies report hyperactivity of the HPA axis following early life adversity. Both the timing of the stressor (Bosch *et al.*, 2012) and the type of stressor (Essex *et al.*, 2011) may play a role for such long-term effects on HPA axis function.

4.2 Cortisol and psychotic symptoms and syndromes

If, as proposed by the neural diathesis stress model (Walker and Diforio, 1997, Walker *et al.*, 2008), activation of the HPA axis mediates the relation of stress with symptom exacerbation, one would expect to find associations between indices of HPA axis and symptom severity or other important outcome measures. However, as discussed in section 2.3, medication and

diagnostic and sampling criteria inevitably constrain the range of symptom severities represented in clinical research samples, and this is especially true of positive symptom measures in studies of psychosis. Likely related to this limitation, research findings in this area are mixed. While some cross-sectional studies have observed a modest relationship between basal cortisol and psychotic symptom severity (Walker and Diforio, 1997, Walker *et al.*, 2008), several other studies of patient samples have not (Ryan *et al.*, 2004, Venkatasubramanian *et al.*, 2007, Yilmaz *et al.*, 2007, Pruessner *et al.*, 2013b, Dogan Bulut *et al.*, 2016). Studies on the CAR in FEP patients found either no association with symptoms (Mondelli *et al.*, 2010a, Pruessner *et al.*, 2013b) or only a trend level relationship between cortisol levels and poor global functioning (Pruessner *et al.*, 2015b). As a measure of cortisol changes over time, hair cortisol concentrations (HCC) over the past three months correlate with general psychopathology (Andrade *et al.*, 2016) and HCC at the time of admission can differentiate between in- and outpatients with psychosis (Streit *et al.*, 2016).

A similarly diverse picture regarding the association between stress and symptoms can be observed in CHR populations. Findings from the North American Prodrome Longitudinal Study (NAPLS) showed small but significant positive correlations between heightened basal cortisol levels and positive, negative, and general symptom severity at baseline (Walker *et al.*, 2013b). A study utilising the ESM method among siblings of patients with psychosis observed that momentary increases in both psychotic symptoms and negative affect were associated with increased cortisol levels in siblings, but not healthy controls (Collip *et al.*, 2011). However, several other cross-sectional studies did not find relationships between cortisol levels and psychotic symptom severity in CHR patients (Sugranyes *et al.*, 2012, Pruessner *et al.*, 2013a, Day *et al.*, 2014). A recent review concluded that a cross-sectional relation between cortisol

levels and measures of psychotic symptom severity could not be confirmed for the majority of studies of individuals at-risk for psychosis, but that there was a more consistent association with anxiety and subjective stress (Karanikas and Garyfallos, 2015). A different picture emerged in a recent longitudinal study, where Walker et al. found that higher baseline cortisol in CHR subjects predicted transition to psychosis over time (Walker *et al.*, 2013b).

In summary, cross-sectional studies in clinical samples of psychotic and CHR patients reveal inconsistent and nonspecific positive relations between cortisol and symptom severity. The findings are consistent with the assumptions that stress and cortisol release have nonspecific effects on the expression of vulnerability for mental illness, and are thus related to multiple symptom dimensions (Belvederi Murri *et al.*, 2012). This pattern is not surprising in light of the varied symptom and HPA axis measures, the diverse samples utilized in this research, and the limitation that the restricted range of positive symptom severity in samples of psychotic and CHR patients reduces statistical power to detect associations with biomarkers. Furthermore, longitudinal studies might have greater power than cross-sectional studies for detecting relations among biomarkers and symptoms.

5. Stress, Glucocorticoids and neuroimaging findings

Structural brain abnormalities are a common finding in psychosis and include reduced total grey and white matter volume in various brain regions as well as increased ventricular volume (Steen *et al.*, 2006, Bora *et al.*, 2011, De Peri *et al.*, 2012, Cannon *et al.*, 2015). Neuroanatomical

abnormalities are already present prior to illness onset among individuals at CHR (Pantelis *et al.*, 2009), and appear to progress over time, especially in those who transition to psychosis (Borgwardt *et al.*, 2008, Takahashi *et al.*, 2009b, Smieskova *et al.*, 2010, Mechelli *et al.*, 2011, Dazzan *et al.*, 2012, Ziermans *et al.*, 2012, Cannon *et al.*, 2015). Moreover, a subset of these neuroanatomical abnormalities (predominately within the temporal lobe) have been observed among children aged 9-13 years within the general population who report subclinical psychotic symptoms (Jacobson *et al.*, 2010, Cullen *et al.*, 2013).

Given the role of certain neuroanatomical regions and endocrine glands in HPA axis regulation, it is assumed that changes in their volume will be associated with indices of HPA axis activity. In particular, hippocampal and pituitary volume (i.e., structures involved in moderating HPA axis activity) would be expected to be linked with measures of HPA axis function, although volume reductions in other regions (e g., amygdala) have also been observed in psychosis (Aas *et al.*, 2012b, Watson *et al.*, 2012). In the following section, we will review the literature on structural abnormalities in psychosis and at risk states for psychosis, with an emphasis on the hippocampus and the pituitary.

5.1 Hippocampal volume abnormalities in psychosis

Hippocampal volume (HV) reduction has emerged as one of the most replicated structural brain abnormalities in psychosis (Velakoulis *et al.*, 2006, Adriano *et al.*, 2012). Hippocampal abnormalities can already be observed at the CHR and FEP stage and there appears to be further shrinkage over time as the disease progresses (Giedd *et al.*, 1999, Velakoulis *et al.*,

1999, Pantelis *et al.*, 2003a). It has been suggested that these changes might be related to hormonal changes in response to the stress of transition to psychosis (Pantelis *et al.*, 2007).

In these early stages, the left hippocampus appears to be more affected by volume decline than the right (Velakoulis *et al.*, 2006, Buehlmann *et al.*, 2010, Malchow *et al.*, 2013). Evidence for the relevance of the left hippocampus in psychosis stems also from studies showing that particularly reduced left HV is correlated with the number of previous psychotic episodes in schizophrenia patients (Hyza *et al.*, 2014) and that CHR patients who later developed psychosis show altered metabolic activity in the left hippocampal head (Wood *et al.*, 2010).

Challenging the notion of a progressive course of brain changes related to illness onset, two recent studies in CHR patients found a decrease in HV independent of transition status (Wood *et al.*, 2010, Walter *et al.*, 2012). Furthermore, reduced HV has been found in healthy co-twins of probands (van Erp *et al.*, 2004) and non-psychotic offspring of schizophrenia patients (Keshavan *et al.*, 2002), demonstrating an influence of genetic and/or shared environmental factors on HV in these individuals. A longitudinal study in FEP patients suggested that volume reduction in the superior temporal cortex and hippocampus might be reversible dependent on remission status (Schaufelberger *et al.*, 2011). This notion is consistent with evidence from research on stress hormone related conditions, such as Cushing's syndrome (McEwen, 1999, Starkman *et al.*, 1999, Starkman *et al.*, 2003). To date, only one study found larger HV to be predictive of transition to psychosis (Phillips *et al.*, 2002).

HV has been found to inversely correlate with both positive and negative symptoms of psychosis (Watson *et al.*, 2012, Brambilla *et al.*, 2013, Mathew *et al.*, 2014). In a longitudinal study, higher baseline positive symptoms were associated with more striatal and HV loss over

time (Ebdrup *et al.*, 2011). A recent study in FEP found that smaller HV bilaterally was significantly related to positive psychotic symptoms and lower levels of functioning only in male but not in female patients (Pruessner *et al.*, 2015b). In schizophrenia patients, volume reductions in hippocampal subfields CA2/3 and CA1 were found to be correlated to positive symptoms (Kuhn *et al.*, 2012). In recent functional magnetic resonance imaging (fMRI) studies in schizophrenia patients, greater resting state activity of the hippocampus was correlated with more negative symptoms (Tregellas *et al.*, 2014), and increased left hippocampal activity during successful encoding of words was related to positive symptoms (Zierhut *et al.*, 2010).

A meta-analyses on voxel-based morphometry (VBM) studies concluded that grey matter volume reductions in limbic system and other structures are more pronounced in male dominated samples of schizophrenia patients compared to gender balanced samples (Bora *et al.*, 2012). While some studies found more pronounced amygdala volume reductions (Gur *et al.*, 2004, Niu *et al.*, 2004, Frazier *et al.*, 2008) and greater severity of ventricular enlargement (Nopoulos *et al.*, 1997) in male compared to female patients, the majority of reports point to a more pronounced HV reduction in male patients, both with chronic schizophrenia (Bryant *et al.*, 1999, Exner *et al.*, 2008, Irle *et al.*, 2011, Adriano *et al.*, 2012, Bora *et al.*, 2012) and FEP (Bogerts *et al.*, 1990, Pruessner *et al.*, 2015b), and recently also in individuals at CHR (Pruessner *et al.*, 2016).

5.2 Hippocampal volume and HPA axis in psychosis

Inverse associations between reduced HV and HPA axis dysregulation have been observed in various conditions including depression, PTSD and aging (Frodl and O'Keane, 2013, Wingenfeld

and Wolf, 2014). This association has been explained by the important role of the hippocampus in the regulation of the HPA axis (McEwen and Gianaros, 2010). At the neuronal level, chronic stress has been shown to cause shortening of dendrites, loss of spine synapses and suppression of neurogenesis in animals. While experimental animal models suggest this can be a reversible process, such cellular alterations are believed to be at the core of HV reductions and the resultant compromise of its role as a regulator of HPA axis function (McEwen and Gianaros, 2010).

Research on the relationship between cortisol levels and brain volume measures in psychosis is limited; a recent study in FEP was the first to report a correlation between higher diurnal cortisol levels and smaller HV in patients, but not in controls (Mondelli *et al.*, 2010b). In contrast, no correlation was observed between cumulative diurnal cortisol exposure and volume in hippocampal subregions in a small sample of FEP patients (Gunduz-Bruce *et al.*, 2007). Subsequently, Pruessner et al. found a greater blunting of the CAR and smaller left HV particularly in male FEP patients (Pruessner *et al.*, 2015b) and individuals at CHR for psychosis (Pruessner *et al.*, 2016), and observed a significant relationship between both markers. No such association was observed in the healthy controls (Pruessner *et al.*, 2015b, Pruessner *et al.*, 2016). Another recent study in CHR individuals using voxel-based morphometry found an association between an attenuated CAR and gray matter volume in parahippocampal / fusiform and parietal areas (Valli *et al.*, 2016). A relationship between the CAR and HV was observed across both groups (CHR and controls) (Valli *et al.*, 2016). In healthy GHR subjects, those with a smaller HV exhibited greater momentary cortisol levels assessed with the experience sampling method (Collip *et al.*, 2013). In summary, initial evidence supports the notion that, similar to findings in other conditions, abnormalities in HPA axis regulation are associated with HV

decline. Future studies need to further investigate the implications of HV and HPA axis dysregulations as related markers of stress vulnerability in psychosis.

5.3 Pituitary volume abnormalities in psychosis

Cross-sectional studies indicate that pituitary volume abnormalities are present at different stages of psychosis but that the pattern of abnormalities (i.e., relative increases/decreases in volume compared to healthy controls) may change over the course of illness. Specifically, studies of first-episode psychosis patients have observed enlarged pituitary volume relative to healthy controls (Pariante *et al.*, 2004, Pariante *et al.*, 2005, Büschlen *et al.*, 2011, Takahashi *et al.*, 2011). In contrast, smaller pituitary volumes relative to controls have been reported among patients with chronic schizophrenia (Pariante *et al.*, 2004, Upadhyaya *et al.*, 2007). However, other studies have observed no pituitary volume abnormalities among patients with psychosis (chronic or first-episode) and healthy controls (Nicolo *et al.*, 2010, Klomp *et al.*, 2012). Furthermore, longitudinal studies following individuals from the time of their first psychotic episode have observed both pituitary volume increases (MacMaster *et al.*, 2007a) and decreases (Nicolo *et al.*, 2010) following antipsychotic treatment. These inconsistent findings may relate to differences in medication types across studies, but could also be related to sex differences and age effects. Pituitary volume has been shown to be larger in women compared to men, and increases with age are more pronounced in female patients (Doraiswamy *et al.*, 1992, MacMaster *et al.*, 2007b). Such sex differences are also present in schizophrenia spectrum disorders (Romo-Nava *et al.*, 2013). Thus, the extent to which the pattern of pituitary volume abnormalities distinguishes individuals with first-episode psychosis from those with chronic illness is currently unclear.

There is limited evidence that GHR individuals are also characterized by pituitary volume abnormalities. While one study of older adult relatives (predominately parents) of individuals with schizophrenia reported enlarged pituitary volume in this group compared to healthy controls (Mondelli *et al.*, 2008); three subsequent studies of younger relatives (including children, adolescents, and young adults) found no such abnormalities (Habets *et al.*, 2012, Cullen *et al.*, 2015a, Shah *et al.*, 2015a). However, Shah and colleagues (2015) observed larger pituitary volume among GHR adolescents and young adults who later converted to psychosis compared to both relatives who did not convert and healthy controls.

Heterogeneous findings have also been reported among individuals at CHR, possibly reflecting differences in symptom severity and medication use across studies. While larger pituitary volume was observed among patients with SPD recruited from psychiatric services (85% of whom were treated with antipsychotic medication) relative to healthy controls (Takahashi *et al.*, 2009a), a subsequent study reported smaller pituitary volume among male (but not female) medication-naïve SPD patients when compared to controls (Romo-Nava *et al.*, 2013). Of the four studies to have examined pituitary volume in CHR youth relative to controls (Garner *et al.*, 2005, Büschlen *et al.*, 2011, Takahashi *et al.*, 2013, Walter *et al.*, 2014) only one (Takahashi *et al.*, 2013) observed significant group differences (enlarged pituitary among CHR youth). While CHR youth in all four samples were antipsychotic-naïve or minimally-treated, negative symptoms were notably higher among CHR participants in the study by Takahashi at colleagues, possibly reflecting more advanced illness. Moreover, while two of these studies reported that CHR youth who transitioned to psychosis within 1-3 years were characterized by larger pituitary volumes at study commencement compared to CHR individuals who did not (Garner *et al.*, 2005, Büschlen *et al.*, 2011), these findings were not replicated in the two subsequent

investigations (Takahashi *et al.*, 2013, Walter *et al.*, 2014), possibly reflecting limited statistical power related to the small number of participants in the transitioned groups. Finally, no pituitary volume abnormalities were observed in a sample of children (11-14 years) at elevated risk for schizophrenia due to the presence of developmental antecedents of the disorder (Cullen *et al.*, 2015b).

Findings to date therefore tentatively suggest that pituitary volume abnormalities may not be present during the early stages of illness but may reflect more advanced or acute illness. However, it is important to note that, with the exception of one study of GHR youth, in which a positive association between pituitary volume and schizotypal symptoms was observed (Shah *et al.*, 2015b), previous studies of at-risk individuals have failed to observe a correlation between increased pituitary volume and more severe symptoms, including positive and negative psychotic symptoms, anxiety, and depression (Garner *et al.*, 2005, Mondelli *et al.*, 2008, Takahashi *et al.*, 2009a, Takahashi *et al.*, 2013, Walter *et al.*, 2014).

5.4 Pituitary volume and HPA axis function

While it is hypothesized that the pituitary volume enlargements characterizing FEP patients and (some) at-risk individuals result in HPA hyperactivity, following an increase in the size and number of anterior pituitary corticotroph cells responsible for producing HPA axis hormones (Pariante, 2008), there is scant evidence to support this. In fact, the relationship between pituitary volume and cortisol levels has scarcely been examined among individuals with or at-risk for psychosis, or among healthy individuals.

An early study of patients with depression reported that pituitary volume was positively associated with post-dexamethasone plasma cortisol levels after adjusting for age and sex (Axelson *et al.*, 1992). However, more recently, studies of GHR individuals (Habets *et al.*, 2012) and CHR youth (Thompson *et al.*, 2007b) have observed no relationship between pituitary volume and daytime cortisol levels. Interestingly, a study of healthy adolescents recently reported that pituitary volume was positively associated with the CAR and negatively associated with daytime cortisol levels (Kaess *et al.*, 2013); though both relationships were present only in males. Thus, it is possible that differences in the sex ratio of participants across studies may contribute to the heterogeneity of findings. Further work is needed to determine whether pituitary volume is reliably associated with HPA activity.

Conflicting results have also been obtained in the few studies that examined the relationship between pituitary volume and experiences of psychosocial stress. One study using the ESM technique to assess emotional reactivity to stress (i.e., self-reported increases in negative affect in response to daily social stressors) reported a *positive* association between pituitary volume and stress reactivity among patients with psychotic disorder that was not present among their first-degree relatives or healthy controls (Habets *et al.*, 2012). In contrast, a recent study of children aged 11-14 years reported that pituitary volume was *negatively* associated with both exposure to physical punishment and distress relating to other negative life events among children with a family history of schizophrenia (Cullen *et al.*, 2015b). These associations were not, however, present among children at-risk due to developmental antecedents of schizophrenia or typically-developing children. Interestingly, this latter finding is consistent with a previous study of adolescents with borderline personality disorder, in which those exposed to childhood maltreatment were characterized by smaller pituitary volumes compared to

unexposed youth (Garner *et al.*, 2007). In summary, there is no consistent evidence to suggest a relationship between pituitary volume with cortisol or psychosocial stress among those with, and at-risk for, psychosis, and further research is needed.

6. Stress, Glucocorticoids and Cognitive function

Neurocognitive dysfunction is a core feature of schizophrenia and other psychotic disorders. Relative to healthy individuals, patients are characterized by moderate-to-large deficits across multiple neurocognitive domains, with the most severe impairments observed in memory and executive function (Reichenberg and Harvey, 2007). Similar impairments, albeit smaller in magnitude, have also been observed among individuals at CHR (Fusar-Poli *et al.*, 2012b), GHR adolescents and young adults (Agnew-Blais and Seidman, 2013) and children presenting developmental antecedents of schizophrenia (Cullen *et al.*, 2010, Dickson *et al.*, 2014). While it is likely that these neurocognitive deficits are influenced by genetic factors (Kahn and Keefe, 2013), there is some evidence to suggest that psychosocial stress exposure and abnormal HPA axis function may be contributors.

Animal studies indicate that stress-induced HPA axis dysfunction can lead to structural abnormalities in the hippocampus and medial prefrontal cortex, regions which are known to play a crucial role in mediating HPA axis function (Herman *et al.*, 2005). Specifically, studies of rodents have observed that chronic stress and persistently-elevated glucocorticoid levels can cause hippocampal cell damage (Sapolsky, 2000), and are associated with structural changes in the medial prefrontal cortex (Cerqueira *et al.*, 2008). Thus, the deficits in memory and executive

function that have been consistently observed among individuals with psychosis, may, at least in part, be due to the adverse effects of psychosocial stress and cortisol on the brain regions that support these neurocognitive functions. In support of this notion, elevated cortisol levels have been associated with poorer performance on tests of memory and executive function among individuals with schizophrenia (Walder *et al.*, 2000), and a more blunted CAR has been found to correlate with greater deficits in verbal memory in FEP (Aas *et al.*, 2011b). Furthermore, a study of children at elevated risk for schizophrenia (due to either a family history of illness or developmental antecedents of schizophrenia) observed that poorer performance on memory and executive function measures was associated with more abnormal cortisol levels (i.e., elevated baseline cortisol levels and a more blunted CAR) among at-risk children, but not typically-developing children (Cullen *et al.*, 2014b).

As noted above, one possible explanation for the association of cognitive performance with cortisol among individuals with, and at-risk for, psychosis is that HPA axis dysfunction, caused by exposure and/or reactivity to psychosocial stress, may have a direct effect on these cognitive abilities via the effects of cortisol on the brain structures supporting these functions. However, the extent to which the observed associations between neurocognitive functions and cortisol are triggered by psychosocial stress exposure is currently unclear. While some studies of individuals with schizophrenia have reported greater impairments in memory and executive function among those exposed to childhood maltreatment (Lysaker *et al.*, 2001, Aas *et al.*, 2011a, Shannon *et al.*, 2011, Aas *et al.*, 2012b), other studies have observed no association between psychosocial stress exposure (including childhood maltreatment) and neurocognitive deficits among individuals with psychosis (Schenkel *et al.*, 2005, Aas *et al.*, 2011c, Sideli *et al.*,

2014). Indeed, Aas and colleagues reported that psychosocial stress exposure (childhood trauma, stressful life events, and perceived stress) was associated with poorer neurocognitive function among healthy individuals, but not among individuals with first-episode psychosis (Aas *et al.*, 2011b), a finding that was replicated in a larger investigation of FEP patients in this study (Sideli *et al.*, 2014). A similar association was observed in a study of schizophrenia patients (McCabe *et al.*, 2012), in which a negative relationship was reported between exposure to childhood adversity and IQ among healthy controls, but not among patients. However, in two different studies, Aas and colleagues observed that childhood trauma was correlated with poorer neurocognitive performance in chronic schizophrenia and bipolar patients (Aas *et al.*, 2012c) and among male FEP and affective psychosis patients (Aas *et al.*, 2011a). Thus, the inconsistency in findings across studies may be due to variability in patient characteristics across studies and/or differences in the specific psychosocial stressors examined.

The lack of consistent findings of an association between psychosocial stress and cognitive function suggests that, if abnormal cortisol levels do directly contribute to neurocognitive deficits in individuals with psychosis, this may not be driven by increased exposure or reactivity to psychosocial stressors. Alternatively, the association between neurocognitive function and cortisol levels observed in those with, and at-risk for, psychosis may be indirect. Indeed, it is possible that the association reflects underlying dysfunction in the hippocampus and medial prefrontal cortex, regions which are densely populated with glucocorticoid receptors and known to play a crucial role in mediating HPA axis function (Herman *et al.*, 2005). Thus, among those with, or on the trajectory to, psychosis, abnormal neurodevelopmental processes (possibly triggered by genetic factors or early environmental insults) may have affected the functional integrity of the brain structures that mediate both HPA axis function and

neurocognitive performance, thereby resulting in the observed correlations between these two features of psychosis.

7. Stress, Glucocorticoids and Neurotransmitters in Psychosis

Recent neuroimaging research has provided greater insights into dopamine (DA) activity and its relation with stress and HPA function in psychosis. Increased DA synthesis capacity and release are reported in both psychotic patients (Howes *et al.*, 2009a, Lyon *et al.*, 2011, Howes *et al.*, 2012b) and in CHR patients who subsequently develop a frank psychotic illness (Howes *et al.*, 2009b, Howes *et al.*, 2011a, Howes *et al.*, 2011b). Particularly high levels of DA in the striatum have been associated with positive symptom severity (such as hallucinations and delusions) as well as risk of relapse in psychosis (Kapur, 2003), consistent with evidence that drugs that increase DA release have the potential to induce or worsen psychosis (Lieberman *et al.*, 1987, Howes *et al.*, 2012a). Interestingly, a recent study found no significant difference in striatal DA levels between healthy controls and patients with treatment-resistant psychosis (i.e., patients who fail to show improvements in response to antipsychotic medications), indicating that other neurotransmitters systems may also contribute to symptom severity in psychosis (Demjaha *et al.*, 2012).

Increased DA levels in the striatum in patients with psychosis may be secondary to elevated glucocorticoid levels. Animal studies support this theory by showing an association between stress and DA release in the mesolimbic area of the brain (Schatzberg *et al.*, 1985, Rouge-Pont

et al., 1993). A recent PET study by Mizrahi and colleagues (Mizrahi *et al.*, 2012) aimed to clarify the relationship between stress and DA levels in psychosis: Twelve individuals at CHR for psychosis, 10 with FEP and 12 matched healthy controls underwent measures of cortisol as well as DA levels during a control task and a psychosocial stress task, the Montreal Imaging Stress Task (MIST) (Dedovic *et al.*, 2005). Stress-induced DA increase in the striatum was significantly greater in both patients with FEP and individuals at CHR when compared to healthy controls. Consistent with this, changes in cortisol AUC showed significant group differences, with the psychotic group demonstrating the largest cortisol response to stress, and the CHR group midway between the controls and FEP group. Further, the percentage difference in cortisol between the control and stress tasks was significantly associated with PET indices of striatal DA, suggesting a direct relationship between stress induced DA release and salivary cortisol.

A pathologic response to life stressors, in which a hyper-responsive dopaminergic system is thought to play a key role, is a potential etiologic factor in triggering psychotic symptoms and relapses in psychosis. In this context, it has been argued that treating high risk individuals with neuroleptics known to target DA activation in the brain may prevent or delay transition to psychosis (McGorry *et al.*, 2002, McGlashan *et al.*, 2006). However, this approach is highly controversial in light of the well-known side effects of antipsychotic medication and the comparable or even superior benefits of psychosocial interventions at the high risk stage (McGorry *et al.*, 2009, Liu and Demjaha, 2013, Woods *et al.*, 2013).

It has been documented that social and environmental adversities, such as early traumatic events, social isolation, being an immigrant, or living in a big city may be important causes of

stress sensitization via a long-term dysregulation of DA systems (Howes and Murray, 2014). Such stress sensitization is evident in increased emotional reactivity to daily stress in adult life, which might result in further increases of DA levels, presumably constituting the link between stress and relapses in psychosis. All these risk factors have been included in a multi-environmental social defeat model of psychosis risk (van Winkel *et al.*, 2008), showing that social defeat stress leads to abnormalities in the dopaminergic neurotransmission.

Investigating the link between abnormal DA release and adverse early life experiences, one study had screened 105 college students for childhood parental bonding, and five participants from the top and five from the bottom range were chosen to take part in a PET study (Pruessner *et al.*, 2004). Individuals with low parental care showed increased midbrain DA release, and DA release was significantly correlated with cortisol levels in response to stress (Pruessner *et al.*, 2004). These findings suggest that childhood adverse events are associated with an increase in mesolimbic DA levels in humans.

In addition to DA abnormalities, researchers have described glutamatergic abnormalities in schizophrenia, which might also be modulated by stress exposure, including early trauma. Recent studies show associations between increased stress and glucocorticoid effects on glutamate transmission, including glutamate release, glutamate receptors and glutamate clearance and metabolism (Popoli *et al.*, 2012). Glutamate has also been linked to treatment resistance in psychosis: Patients with treatment resistant illness did not show the elevated dopamine synthesis capacity in the striatum that is usually found in psychosis, but showed elevated glutamate levels in the anterior cortex compared to healthy controls (Demjaha *et al.*,

2012, Demjaha *et al.*, 2014). Thus, excess striatal DA synthesis is likely not the final common pathway in all psychotic individuals.

Moreover, in some cases, elevated striatal DA levels might be driven by abnormalities in hippocampal glutamatergic neurotransmission. In a study of patients at CHR for psychosis, reduced hippocampal glutamate levels were associated with increased striatal DA uptake, which in turn was related to the severity of abnormal beliefs (Stone *et al.*, 2010). This has led to the suggestion that an altered relationship between hippocampal glutamate and striatal DA systems may increase the risk for transition to psychosis (Stone *et al.*, 2010). In an attempt to integrate these findings, it has been proposed that there are at least two possible explanations for the involvement of both dopamine and glutamate in psychosis (Howes *et al.*, 2015); one, that these neurotransmitters are related to different subtypes of the disorder (i.e., glutamate abnormalities being a feature of treatment resistant psychosis), and two, that they contribute to different features of schizophrenia (i.e., dopamine abnormalities giving rise to the positive symptoms of psychosis whilst glutamatergic dysfunction underlies the negative and cognitive symptoms).

8. Genetic vulnerability markers and psychosis

8.1 Genetic factors and early adversity

Psychosis is assumed to be a disorder with polygenic origins (Smoller and Finn, 2003, Giusti-Rodriguez and Sullivan, 2013, Tesli *et al.*, 2014) and shared genetic risk factors with bipolar disorder (Lichtenstein *et al.*, 2009). Moreover, environmental risk and gene by environment

interactions are assumed to account for a substantial portion of the phenotypic variance. Recent studies focusing on gene-environment interactions between early life adversity and genetic vulnerability for psychosis lend support to this assumption (Vaillant and Schnurr, 1988, van Winkel *et al.*, 2013). For example, for the brain-derived neurotrophic factor (BDNF) gene val66met, adult met carriers from the general population have greater increases in psychotic symptoms following stress, when compared to val/val carriers (Alemany *et al.*, 2011). In individuals at GHR for affective disorder, Met carriers of the BDNF val66met also show an increased stress response to objectively stressful events compared to val/val carriers (Vinberg *et al.*, 2009), and in a large sample of patients with psychotic disorders, *met* carriers with high levels of childhood trauma had the lowest BDNF mRNA levels. (Mondelli *et al.*, 2011, Aas *et al.*, 2014b). These findings indicate that met carriers are more vulnerable to early trauma than val/val carriers. In fact, two recent studies in patients with psychosis show that met carriers exposed to childhood trauma have reduced cognitive function as well as a reduced volume of the dentate gyrus, a region in the hippocampus which is sensitive to stress and involved in neurogenesis (Aas *et al.*, 2013, Aas *et al.*, 2014b).

Another risk gene related to increased stress reactivity is the serotonin transporter gene, specifically, the 5-HTTLPR functional polymorphism found in the promoter region of the 5-HTT/SLC6A4. A large body of research demonstrates a relationship between variations in 5-HTTLPR and the degree of the endocrine stress response (O'Hara and Hallmayer, 2007, Caspi *et al.*, 2010). Interestingly, a higher cortisol response in s-allele carriers has been observed in healthy newborns (Mueller *et al.*, 2010). Similarly, the serotonin transporter gene has been shown to modulate the effect of childhood trauma on cognitive function in patients with a psychotic illness, where patients carrying the ss genotype were more vulnerable to the negative

effect of trauma than ll and sl carriers (Aas *et al.*, 2012a). Other commonly studied stress related genes are the FKBP5 gene (Klengel *et al.*, 2013), and the glucocorticoid receptor gene, also called the NR3C1. Both genes are linked to long-term changes in the HPA axis following early stressful events.

The studies described above provide further support for the neural-diathesis stress model by presenting evidence for the biological link between stress and DA activation and between genetic factors and stress vulnerability. However, it remains largely unexplored how genes are associated with DA release in response to stress (early adverse events or acute stress). A promising novel method for estimating the cumulative genetic risk of psychosis has been developed with a recent molecular validation of the psychosis continuum model (Bigdeli *et al.*, 2014, Tesli *et al.*, 2014), providing a new tool to untangle the effects of genetic and environmental risk factors in psychosis. The polygenic risk score is calculated based on large genome-wide association studies of additional explained genetic variance previously classified as 'missing' (Iyegbe *et al.*, 2014). An important next step is to investigate whether the polygenetic risk score for psychosis is linked to HPA axis activity and DA release in response to stressful events.

8.2 Stress, glucocorticoids and epigenetic processes

The term 'Epigenetics' refers to cellular factors and processes (e.g., DNA methylation, histone modification) that influence how our genes are expressed, without changing the actual DNA sequence genes. Recent research indicates that stressful events occurring in early life can cause long-term neurobiological changes and alterations in genes related to the HPA axis (Heim *et al.*,

2000b, Heim *et al.*, 2008, Heim *et al.*, 2010, Klengel *et al.*, 2013). For example, low maternal care in rodents has been linked to methylation of the promotor region of the glucocorticoid receptor (GR) gene and increased hormonal (corticosterone) responses to stress. (Weaver *et al.*, 2004, Weaver, 2007, Champagne and Curley, 2009). A review examining the effects of early life stress on epigenetic modifications in humans concluded that DNA methylation may be critical to these processes (Champagne and Curley, 2009).

More recently, it has been reported that childhood trauma is associated with increased glucocorticoid receptor (GR) gene promoter methylation and attenuated responses to the dexamethasone suppression test (Tyrka *et al.*, 2012). Another study has additionally linked childhood trauma to altered methylation of the FKBP5 gene and long-term dysregulation of the stress hormone system in adult humans (Klengel *et al.*, 2013), supporting the notion that stress may induce epigenetic effects on biological systems regulating the stress hormone release.

Stress exposure in the perinatal period has also been related to a reduction in BDNF in the brain of adult rats (Riva, 2013), and it was proposed that epigenetic changes (i.e., an increase in methylation) caused by perinatal stress may contribute to reduced transcription of the BDNF gene and cognitive changes. It has also been postulated that different epigenetic changes relate to perinatal stress in animals in many genes, including those linked to schizophrenia and bipolar disorders (such as CACNA1C, DISC1, and COMT). It is therefore important to investigate the effect of stress on gene expression, not only on single genes, but across the genome to further understand how stress can alter gene expression in schizophrenia.

9. Stress, glucocorticoids and inflammatory processes

Recent studies have implicated the immune system in the development of psychopathology with increased inflammation reported among individuals with depression (Leonard, 2001, 2007, Zunszain *et al.*, 2011), schizophrenia, and bipolar disorder (Hope *et al.*, 2009, Dieset *et al.*, 2012). Consistent with this, genome-wide association studies (GWAS) clearly indicate immune genes as susceptibility genes for schizophrenia, including the *IL-IB* gene and the major histocompatibility complex (Stefansson *et al.*, 2009, Ripke *et al.*, 2013). Furthermore, prenatal infections (e g., rubella, influenza, and toxoplasmosis) during fetal and early life have been associated with increased risk for severe psychiatric disorders in adulthood (Brown, 2006).

Glucocorticoids, released in response to stressful events, are potent anti-inflammatory hormones in the body (Vinson, 2009); when stressors are acute and time-limited, such as fight-or-flight stressors, there is an adaptive redistribution of cells as the natural immune system prepares for possible infection and/or injury (Segerstrom and Miller, 2004). However, as stressors become chronic, there are changes in the ability of the immune system to adapt. Acute stress versus chronic stress results in a shift from adaptive to maladaptive changes in the immune system. (For an in-depth discussion of chronic versus acute stress and inflammation, see the review paper by (Segerstrom and Miller, 2004).

The HPA axis influences immunological responses via the effect of glucocorticoids on immune and inflammatory reactions, for instance on the cytokines interleukin (IL)-1 and IL-6. Both abnormal glucocorticoid function and increased inflammatory markers (i.e., cytokines and C-

reactive protein) have been recently reported in patients with first-episode psychosis and in bipolar disorders (Potvin *et al.*, 2008, Hope *et al.*, 2009, Mondelli *et al.*, 2010a, Mondelli *et al.*, 2011). Interestingly, IL-1beta and IL-6 have been indicated to play a central role in synaptic plasticity, neurogenesis and neuromodulation (Zunszain *et al.*, 2011), suggesting that these cytokines may also influence cognitive function. A pilot study of patients with first-episode psychosis and healthy controls found a negative relationship between increased inflammation parameters (IL-8, and IL-6) and cognitive impairments (Aas, 2010), indicating that immune markers are related to cognitive function.

Cognitive deficits are one of the core features in schizophrenia, with a performance that is on average one standard deviation lower than in controls across domains and apparent in first-episode psychosis (Aas *et al.*, 2014a). However, little is known regarding the mechanisms behind these impairments. As noted above (section 6), the observed associations between HPA axis function and neurocognitive impairments may reflect a direct effect of cortisol on the brain; here, we propose that at least some of this effect may be mediated by inflammatory processes.

These above findings are consistent with the notion that inflammation is related to reduced BDNF levels (Smith *et al.*, 2012, van Winkel *et al.*, 2013); BDNF is important for growth and differentiation of neurons during brain development, as well as synaptic plasticity and maintenance of neurons in adult life (Lewin and Barde, 1996). As noted, exposure to psychosocial stressors such as childhood trauma is associated with reduction of BDNF RNA levels (Mondelli *et al.*, 2011, Aas *et al.*, 2014b). Indeed, at the cellular level, both acute and

chronically high levels of stress exposure are linked to atrophy of dendrites and suppression of neurogenesis (Sapolsky *et al.*, 1986, Wolf, 2003), likely mediated by stress-based reductions in neurotrophic factors, including BDNF (Calabrese *et al.*, 2009). It is possible that stressors in early life are related to long-term changes in the HPA axis, which in turn is associated with an up-regulation of the pro-inflammatory system. The pro-inflammatory system activation of microglia in the brain could potentially reduce BDNF levels, resulting in both cognitive deficits and brain abnormalities, such as reduced HV in schizophrenia. Further studies are needed to understand the role of inflammatory markers in the cognitive impairments that characterize severe mental disorders. Interestingly, drugs targeting the immune system, such as COX-2 inhibitor (celecoxib) or COX-1/COX-2 inhibitor (aspirin), have recently been reported to significantly improve psychotic symptoms in patients with schizophrenia spectrum disorders, when used as adjunct therapy to antipsychotics (Muller *et al.*, 2002, Akhondzadeh *et al.*, 2007, Muller *et al.*, 2010).

A recent post-mortem study aiming to disentangle the relationship between stress and genes involved in inflammatory pathways showed that the brains of schizophrenia patients were more likely to be characterised by both high stress and high inflammatory markers compared to the brains of bipolar patients and controls (Fillman *et al.*, 2014). There was also a trend for a higher than expected number of bipolar patients in this high stress/high inflammation category compared to controls. The study additionally provided evidence that inflammatory genes were more likely to be associated with schizophrenia whereas stress genes had a greater association with bipolar disorder. These findings suggest the importance of considering interactions

between stress signalling and neuroimmune pathways in the pathophysiological processes in psychosis.

10. Neurodevelopmental processes and sex differences

The idea that neurodevelopmental processes are implicated in the etiology of psychotic disorders is now generally accepted. Although neurodevelopmental models vary in terms of the developmental period (i.e., prenatal versus early postnatal or adolescence) and the mechanisms (i.e., prenatal versus early trauma or deviations in normal adolescent neuromaturation) that they emphasize, all share the assumption that the neuropathological process subserving psychosis begins prior to the clinical onset of the disorder (Rapoport *et al.*, 2012, Read *et al.*, 2014, Waltereit *et al.*, 2014). An overview of neurodevelopmental models of psychosis is beyond the scope of this paper, however, it is relevant to note that stress figures prominently in several models.

The "traumagenic" neurodevelopmental model, for example, posits that the biological sequelae of early adversity sets the stage for the neuropathological process that is manifested as clinical psychosis later in life (Read *et al.*, 2014). Others focus on prenatal insults and placental pathology, as well as mutations and rare genetic variants that can contribute to risk for later psychiatric disorder in a diagnostically nonspecific manner (Rapoport *et al.*, 2012). Similarly, the genetic factors that influence developmental changes in synaptic plasticity have been hypothesized to play a key role for mental health outcomes (Waltereit *et al.*, 2014). Other models have placed a greater emphasis on later developmental processes, including normative

increases in stress-sensitivity and HPA activation associated with adolescence (Holtzman *et al.*, 2013, Walker, 2008 #3729). Related to these post-pubertal processes, recent neurodevelopmental models have attempted to account for the well-established sex differences in premorbid and prodromal manifestations of risk for psychosis (Baldwin and Srivastava, 2015).

It is possible that sex differences in brain development are at the core of the prominent sex differences in the clinical picture in psychosis and determine sex specific findings in HPA axis function and related brain and endocrine structures (see sections 2.6 and 3.5). Interestingly, sex differences in brain morphology in schizophrenia occur in areas that normally show sexual dimorphism, with some studies even pointing to a reversal of normal patterns of sexual differentiation in the brains of patients (Goldstein *et al.*, 2002, Gur *et al.*, 2004, Abel *et al.*, 2010). In other words, the same factors that control normal sexual dimorphisms may underlie the neuropathological processes leading to psychosis.

Exposure to gonadal hormones during critical pre-, peri-, and postnatal stages is known to shape sex differences in brain morphology and HPA function. Stressful events and insults during these critical neurodevelopmental phases might thus have a different impact on neuropathologic processes in men and women (Goel *et al.*, 2014). In particular, higher levels of estrogen are believed to constitute a protective effect at different stages of psychosis etiology in women and the lack this hormone constitutes a relative disadvantage in men. Estrogen effects range from sexual differentiation of the brain (Seeman, 1997, McEwen, 2002, Hafner, 2003, Seeman, 2008, Abel *et al.*, 2010), to shaping the HPA axis response to stress (Kirschbaum *et al.*, 1999, Handa and Weiser, 2014) to exerting ameliorating effects on psychotic symptoms (Riecher-Rossler and Hafner, 1993, Hafner, 2003).

Subsequent sex specific influences on brain maturation and HPA axis regulation occur later in life (at the time of puberty and adulthood) and are believed to interact with the consequences of early neurodevelopmental insults. Such factors can cause further progression of brain abnormalities and are often associated with the onset of psychosis (Pantelis *et al.*, 2003b, Phillips *et al.*, 2006, McCormick and Mathews, 2007). For example, male compared to female patients frequently have a history of poorer premorbid adjustment, show lower levels of social development related to an earlier age of illness onset, exhibit more negative symptoms and have higher rates of substance use (Seeman, 2008, Ochoa *et al.*, 2012). Furthermore, psychotic episodes themselves are considered "neurotoxic" (McGlashan and Johannessen, 1996) which could initiate additional harmful processes, especially in the brains of male patients.

11. Discussion

In this article, we have reviewed recent findings on stress and HPA axis functioning relevant to the neural diathesis-stress model of psychosis (Walker and Diforio, 1997, Walker *et al.*, 2008). The review has provided a basis for validating elements of the original model and for extending the model to encompass more nuanced aspects of the potential role of stress and HPA axis function in the neuropathological processes involved in psychosis. In addition, the recent research findings have highlighted some of the complexities and challenges in this area of investigation. In this final chapter, we will summarize the insights from the investigation of HPA axis function in psychosis and CHR populations over the past decade and briefly explore the lessons learned from glucocorticoid induced psychosis for the causal relationship between

elevated glucocorticoid levels and psychotic symptoms, before presenting an extended neural diathesis stress model of schizophrenia and concluding with implications for future research and treatment strategies.

11.1 Summary of HPA axis findings

With regard to the elements of the original model, there is now additional evidence of elevated baseline cortisol in psychotic patients, especially for those who are *not on antipsychotic medication*. In fact, studies reported in the past decade have concluded, with few exceptions, that 1) atypical antipsychotics reduce basal cortisol levels (Cohrs *et al.*, 2006) and 2) that the magnitude of cortisol reduction is associated with symptom severity reduction (Zhang *et al.*, 2005). Thus suppression of basal cortisol secretion may be a mechanism of antipsychotic action for some patients. Interestingly, it has recently been shown that patients with lower CAR show a less favourable response to antipsychotics (Mondelli *et al.*, 2015), suggesting that CAR and basal cortisol levels are subserved by different mechanisms.

In addition, there is now greater evidence that elevations in basal cortisol can be observed in CHR youth who, by definition, manifest attenuated positive symptoms. Moreover, as is the case with diagnosed psychotic patients, it appears that antipsychotic medication reduces cortisol levels in CHR subjects (Sugranyes *et al.*, 2012). In contrast to findings from CHR samples, studies of subjects at GHR for psychosis were less likely to yield evidence of elevated cortisol. This would be expected, assuming that basal HPA hyperactivity is a risk factor for serious mental illness and that the representation of pre-psychotic individuals in GHR samples is lower than in CHR samples.

Cross sectional studies have not provided credible evidence for a relation between HPA axis changes and symptom severity. However, recent research indicates that higher cortisol is linked with a greater likelihood of conversion to psychosis, supporting our discussion in section 2.4, that longitudinal studies provide greater power for detecting effects and greater potential for inferring causation.

In contrast to basal levels, a non-elevated or blunted response to acute stress has typically been reported in both established psychosis and in individuals at CHR for psychosis. The same conclusion was drawn in a recent review of research on stress and FEP (Borges *et al.*, 2013). This pattern parallels findings of a blunted cortisol response to negative events and challenge tests in depressed patients, who are generally characterized by elevated baseline cortisol levels (Peeters *et al.*, 2003). The dissociation of basal cortisol from stress-induced cortisol is not a novel finding. While one study reported an inverse association between basal and stress-induced levels (Miller *et al.*, 2013) and another investigation revealed a positive relation (Kidd *et al.*, 2014), the majority of reports indicate no significant relationship in healthy children (Dietz *et al.*, 2013) and adults (Miller *et al.*, 2011, Tomiyama *et al.*, 2012). Similarly basal cortisol has been found to be unrelated to ACTH-induced cortisol responses (Bollaert *et al.*, 2003, de Jong *et al.*, 2007).

In addition to the absence of an augmented cortisol response to acute challenge, the accumulating literature suggests that a blunted CAR characterizes diagnosed psychotic patients, with conflicting reports in CHR samples (Berger *et al.*, 2016). While the latter could be explained by the heterogeneity of the clinical picture in CHR populations and the relatively small numbers of converters to psychosis (Fusar-Poli *et al.*, 2012a), measuring the CAR is challenging, and the

determinants are not yet fully understood (Stalder *et al.*, 2016). It appears that the CAR is independent of daytime basal cortisol levels (Fries *et al.*, 2009; Wilhelm *et al.*, 2007; (Laceulle *et al.*, 2015) and of stress-induced cortisol (Kidd *et al.*, 2014, Laceulle *et al.*, 2015). Although this independence of various cortisol indices is not explicable by the law of initial value (see 2.8.3), both elevated basal cortisol levels and attenuated cortisol levels to stress and awakening are likely the consequence of a general dysregulation of the HPA axis. In support of this notion, it has been proposed that attenuated cortisol responses are the consequence of a prolonged period of hyperactivity of the hypothalamic-pituitary-adrenal axis due to chronic stress (Heim *et al.*, 2000a, Fries *et al.*, 2005). While the experience of psychosis could have constituted such a chronic stressor, the experience for CHR individuals will likely have been less chronic. It can be assumed that the underlying mechanisms determining elevated cortisol levels at baseline and attenuated responses to stimulation differ and that their interplay is complex. In the context of hypocortisolism, dysregulations on several levels of the HPA axis have been discussed, such as reduced adrenocortical sensitivity to ACTH (Schmidt-Reinwald *et al.*, 1999, Rohleder *et al.*, 2003, Meinlschmidt and Heim, 2005), down-regulation of CRF receptors in the pituitary causing blunted ACTH responses, increased feedback sensitivity of the HPA axis, and morphological changes (Heim *et al.*, 2000a). Furthermore, findings of a missing CAR and cortisol response to psychosocial stress in patients with hippocampal damage (in the context of a normal diurnal patters) suggest that hippocampal integrity is crucial for HPA axis responsiveness but not for basal cortisol (Buchanan *et al.*, 2004, Wolf *et al.*, 2005, Buchanan *et al.*, 2009).

A lesson that can be learned from the incongruent findings is that differences in various indices of HPA axis activation must be taken into consideration and incorporated into models when conceptualizing the role of stress and the HPA axis in the etiology of psychosis. Furthermore, it

is clear that the origin of the HPA axis dysregulation cannot be determined through studies using salivary cortisol alone, since many levels and secretagogues of this complex system can be involved (Binder and Holsboer, 2012). Additional research examining the relationship between various HPA axis measures and related brain morphological, receptor level, molecular, genetic and epigenetic changes may provide a better understanding of the complex mechanisms involved in hyper- and hypo-activation and help to explain the inconsistent findings.

11.2 What can we learn from glucocorticoid induced psychosis?

Before turning to a discussion of revisions to the neural diathesis-stress model, it is relevant to first revisit the possibility that the abnormalities of HPA function found to be associated with psychosis are primarily or solely illness-induced; in other words, that elevated cortisol levels are a consequence of the stress associated with the prodromal and clinical symptoms of psychosis. While this is possible, there is now more extensive evidence from several areas of inquiry that elevated cortisol levels do increase the risk of psychosis. The accumulating body of literature on secondary effects of glucocorticoid treatment of illnesses (e g., allergic, inflammatory or auto-immune disorders) (Dubovsky *et al.*, 2012, Ross and Cetas, 2012, Judd *et al.*, 2014, West and Kenedi, 2014) and research on neuropsychiatric complications associated with hypercortisolemia in Cushing's disease (Pivonello *et al.*, 2015) support this view. The incidence of severe psychiatric symptoms following treatment with corticosteroids is estimated to be about 6%, and the incidence of any symptoms about 20% (Dubovsky *et al.*, 2012, Ross and Cetas, 2012). However, these figures are likely to be underestimates as the majority of studies in this field focus on physical side effects, and do not conduct systematic evaluations of the

range of psychiatric symptoms (Dubovsky *et al.*, 2012). Documented steroid-induced symptoms include mania, sleeplessness, anxiety, distractibility, depersonalization, cognitive deficits, and psychosis (Dubovsky *et al.*, 2012). "Steroid-induced psychoses" can range from mild disorientation to frank psychosis, and the risk increases in a dose-response manner, with symptoms usually remitting within several weeks following cessation of steroid treatment (Ross and Cetas, 2012). Similarly, common psychiatric symptoms associated with hypercortisolemia in untreated Cushing's syndrome, include depression, mania, anxiety, cognitive deficits and psychosis (Dubovsky *et al.*, 2012, Pivonello *et al.*, 2015). Again, symptoms usually remit after effective treatment of hypercortisolism, and the decline in salivary cortisol in response to treatment of Cushing's is associated with the resolution of psychosis (Myhill *et al.*, 2008). Further, the psychotic symptoms associated with both steroid administration and Cushing's disease are reduced by antipsychotic medication. Finally, one recent study found that men were more prone to develop psychosis like features such as mania, delirium, confusion and disorientation when exposed to CG treatment compared to women. In contrast, women in this study were more likely to develop depression than men (Fardet *et al.*, 2012). This finding is consistent with the notion that the higher incidence of psychosis and relatively poor outcome in men is a consequence of a higher vulnerability to stress resulting in more severe HPA axis dysregulation.

In addition to providing support for the assumption that heightened cortisol increases risk for psychosis, the above findings also illustrate 1) the nonspecific nature of the effects and 2) the importance of individual differences. Increased cortisol levels are associated with a range of mood, cognitive, and psychotic symptoms, and treatment aimed at reducing elevated cortisol results in significant remission in all symptom domains. Thus adverse effects of stress and

heightened HPA activity are not specific to psychosis. The above findings on steroid treatment and Cushing's disease also clearly illustrate the individual differences in vulnerability to the adverse effects of elevated cortisol. Whether induced by stress, maturational changes, disease processes (e g., Cushing's), or corticosteroid treatment, individuals vary in their responses to elevated glucocorticoids. Only a subgroup develop a psychiatric syndrome and, of these, only a subgroup manifest psychosis. Of course, it is now widely accepted that the aetiology of serious mental disorders is complex, and that no single risk factor or neuropathological process will account for all cases of any diagnostic entity. This certainly holds for HPA abnormalities in psychosis.

11.3 An extended neural-diathesis stress model

Based on the complexity of findings reviewed in this paper, revisions and elaborations on the neural diathesis stress model are presented below. The extended model is not intended to be comprehensive, in that not all potential processes and pathways can be incorporated. It is, however, configured to accommodate the growing trends in the empirical literature on stress, HPA function, and psychosis. It should also be emphasized that the model cannot account for all cases of psychosis, but instead is posited to account for the specific etiologic pathway, which is characterised by glucocorticoid sensitivity. Finally, the processes included in the model are not assumed to be specific to psychosis; similar processes may be involved in the aetiology of other psychiatric disorders. The nature of the disorder is assumed to be determined by a cascade of interactions of these processes with pre-existing and progressive vulnerabilities.

In Figure 1 below, an updated neural diathesis-stress model is illustrated.

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Insert Figure 1

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As shown in Figure 1, beginning in the first column on the left, we hypothesize that, commencing early in life (as early as conception), a range of genetic and environmental factors act, in isolation or in concert, to increase vulnerability for psychosis by setting into motion a vicious cycle of progressive degenerative processes that derail neuromaturation and increase psychosis risk. Genetic predisposition includes inherited risk alleles and genetic mutations. In some cases, genetic predisposition may include genes that are relevant to HPA axis function (e.g., FKBP5 and BDNF). Early life adversity factors include, but are not limited to, pre-, peri- and post-natal stress and insults, childhood trauma, poor parental bonding; Environmental/psychological stressors include stressful life events, low socio-economic status, ethnic minority status, city living, substance use; Resilience factors include social support, self-esteem, coping skills, and antipsychotic medication.

As illustrated in the second column, early or later environmental insults contribute to stress system dysregulations (particularly of the HPA axis) and brain degenerative processes in regions that are involved in modulating HPA axis function (e.g. the hippocampus). Initially minor or subtle deviations from normal neurodevelopment build up to render these physiological

response systems increasingly more susceptible to future stressors. Once homeostasis of the system is disrupted, neurotransmitter, inflammatory and cognitive changes further propagate psychosis-relevant developmental deviations and may lead to epigenetic changes.

Disturbance in HPA axis function that precedes the onset of psychosis (and can act as a trigger for the expression of psychotic symptoms) initially occurs in parallel with the abnormal trajectory of neurodevelopment that lays the foundations for the disorder. However, once the HPA axis reaches the point of 'abnormal function', this system interacts with the ongoing neurodevelopmental processes to further propagate psychosis-relevant changes in brain structure and function.

The most dramatic neurodevelopmental and HPA axis changes occur in adolescence, which is the time when prodromal and frank psychotic symptoms most frequently occur for the first time. The onset of puberty then amplifies the neuropathological process because the brain undergoes significant restructuring, and basal activity of the HPA axis increases. Earlier adverse effects of trauma and stress on HPA axis function may then be augmented during the course of post-pubertal maturation by the normative increase in cortisol secretion and the greater divergence of brain structures from the norm among those with greater vulnerability for psychosis, thus rendering the system more susceptible to environmental stressors. A greater magnitude of the HPA axis response during adolescence, may cause environmental stressors, such as substance misuse, adverse experiences and negative life events, to tip the axis into a state of hyperactivity and/or dysregulation characterized by elevated basal cortisol levels, decreased glucocorticoid receptor expression, a blunted CAR, and a dampened cortisol response to stress with consequences for pituitary volume enlargement and hippocampal

volume decline. The manifestation of the HPA axis abnormality is likely dependent on the extent of prior (pre-pubertal) dysregulation and effect modifiers such as sex, coping strategies, and pharmacological treatment.

It is this state of HPA axis abnormality that enhances the ongoing process of neurodevelopmental deviance, initially triggering subthreshold symptoms and eventually resulting in the expression of full psychotic symptoms. There are several ways by which the HPA axis can bring about these changes: (1) HPA axis hyperactivity leads to an increase in cortisol, which then has a damaging effect on specific brain regions, which express high levels of glucocorticoid receptors (i.e., the hippocampus and medial prefrontal cortex (mPFC), thereby leading to impairments in the cognitive abilities attributed to these regions (i.e., memory and executive function), (2) as described previously, the increase in glucocorticoids has the effect of increasing dopamine levels, which in turn gives rise to more prominent psychotic symptoms (perhaps by aberrant attribution of salience to benign stimuli), (3) glucocorticoids, being steroid hormones, lead to epigenetic modifications in key genes which influence brain development (e.g., BDNF) and stress responsivity; thus, further enhancing the pattern of neurodevelopmental abnormality and also influencing the ability of the HPA axis to respond to subsequent stress (perhaps rendering the latter less response to further stimulation including awakening), (4) HPA axis dysfunction leads to glutamatergic abnormalities which may promote the expression of negative symptoms and enhance cognitive deficits, and (5) cross-talk between the HPA axis and the inflammatory system leads to an increase in peripheral inflammation and subsequently neuroinflammation, the latter having further damaging effects on the still developing brain.

Early stages of psychosis progression manifest through poor functioning and behavioral abnormalities and later through psychotic antecedents during childhood. The experience of prodromal or psychotic symptoms can cause significant psychological and environmental distress and has the potential to aggravate the cascade of neurobiological disturbances.

Resilience factors such as social support and psychosocial interventions to increase self-esteem and promote efficient stress management strategies might dampen the vigor of the stress-vulnerability cycle. Following the first psychotic episode, effective treatment with antipsychotic agents may normalize basal cortisol; however, other disturbances in HPA activity (i.e., attenuated response to psychosocial stress or awakening) may persist. In addition, while antipsychotic treatments may reduce dopamine activity, thereby ameliorating psychotic symptoms, other features (e.g., glutamatergic dysfunction, cognitive deficits, neuroanatomical abnormalities, and inflammation) may not improve or may even worsen over time.

11.4 Implications for future research

Compared to the original model formulated almost two decades ago, the extended neural diathesis stress model of schizophrenia includes new and refined definitions of markers and mediators of stress vulnerability in psychosis, which have the potential to guide future research endeavors in the field of stress and psychosis and delineate the starting points for alternative treatment strategies. Many of the suggested future lines of research and treatment will be relevant across clinical domains.

One important avenue of future research suggested by the presented findings is the investigation of associations between various markers of HPA axis activity (i.e. basal cortisol,

cortisol awakening response, cortisol response to stress and various challenge tests) employing intra-individual and longitudinal designs. Such research is expected to provide a better understanding of the relevance and interplay of these various markers, id in the explanation of hitherto conflicting findings, and improve our understanding of the specific profile of HPA axis abnormalities in psychosis.

This research may furthermore result in recommendations for the most appropriate measures of HPA axis function and consensus guidelines for best practice assessment of these markers. Such consensus guidelines have recently been published for the CAR (Stalder *et al.*, 2016). This paper also showcases the many complexities in the assessment of just one of the various measures of HPA axis function. In this context the best possible control for common confounding factors, including such measures as menstrual cycle phase in women, the time of awakening and circadian rhythm, should be aspired.

As outlined in section 2.2, there is evidence for a complex interplay between the HPA axis and the SAM system. A closer inspection of various physiological stress responses and their interaction in the field of psychosis will likely provide a more complete understanding of both short- and long-term stress effects on illness onset and progression. Such research might also resolve the frequently observed discrepancy between perceived stress and physiological stress responses.

Animal studies and human imaging studies can provide insight into gene expression, brain substrates, molecular and receptor related changes associated with stress experiences, HPA axis and clinical outcome measures. Ideally, various additional measures related to stress vulnerability and psychosis progression (i.e. brain structure and function, dopamine, glutamate,

immune function, genetic factors, sex differences, cognition) would be assessed within the same patient study. While this might be challenging due to the often small patient populations at single sites, especially in clinical high risk populations, efforts should be made for researchers to link data acquisition and analysis in populations with comparable intake criteria and assessment protocols, thus ensuring sufficient sample sizes allowing for multifactorial analyses.

One of the most crucial and challenging research questions is how findings on stress and related neurobiological changes can contribute to the prevention of psychosis. Accumulating research on clinical high-risk states has emerged in recent years, and researchers need to continue their efforts to identify common risk and protective factors for conversion to psychosis. While the identification of individuals who are more proximal to psychosis promises the most accurate identification of risk and protective factors and allows the identification of targeted intervention strategies, researchers must also focus on containing the effects of genetic predisposition and early life adversity and their detrimental effects on the stress vulnerability cycle and related progressively increasing psychosis risk. Here, there is a critical need for large-scale population-based observation and intervention studies.

Such longitudinal studies are needed to draw inferences about stress experiences, HPA axis function and other measures of interest on neuromaturational processes and symptomatic outcome over time. They furthermore will allow the identification of different illness trajectories in the presence of various risk and protective factors.

11.5 Implications for treatment strategies

The prevention of onset or exacerbation of psychosis on the basis of knowledge on neurobiological, environmental, psychological and cognitive determinants and consequences of stress is a promising prospect in the face of the often debilitating consequences of psychotic illness and the serious side effects of antipsychotic medication. Especially the normalization of HPA axis function is increasingly viewed as an important therapeutic approach for psychosis and high-risk populations (Garner *et al.*, 2009). As an example, Wolkowitz and colleagues have proposed that elevated GC activity is associated with a down-regulation of GR receptors in the hippocampus, leading to GC resistance, followed by a cascade of events leading to further cellular damage and pathological outcomes (Wolkowitz *et al.*, 2009). The authors propose various treatment strategies to upregulate GR function and correct the metabolic consequences of GR function deficits, including antidepressant medication with certain selective serotonin re-uptake inhibitors (SSRIs), corticotrophic releasining hormone (CRH) antagonists, stress reduction and behavioural interventions, environmental enrichment and exercise. Although anti-glucocorticoid agents have been proven effective for the treatment of some patients with depression (Reus and Wolkowitz, 2001) and a recent review reports some favorable effects of the glucocorticoid receptor antagonist mifepristone on short term positive symptom outcome in psychosis (Garner *et al.*, 2016), there is currently insufficient evidence to conclude that antiglucocorticoid drugs constitute effective treatments for psychosis or even have the potential to prevent the onset of the illness in CHR subjects. Together with some serious side effects of antiglucocorticoid drugs (Reus and Wolkowitz, 2001), a general recommendation for their application seems premature, and additional large-scale studies are

needed to test the efficacy of pharmacological interventions at different levels of the HPA axis (Garner *et al.*, 2009, Garner *et al.*, 2016).

In the meantime, the use of non-pharmacological approaches to reduce stress and increase resiliency towards stress should be the preferred choice of treatment in the early stages of psychosis, especially in high-risk populations. A recent review on psychosocial treatments for psychosis attests to the substantial progress in the use of psychosocial interventions and their effectiveness to reduce stress and improve symptoms and functioning (Mueser *et al.*, 2013). Psychosocial interventions targeting symptoms and psychosocial functioning include cognitive behavioural therapy, family psychoeducation, illness self-management training and social skills-training. Although these interventions are evidence based and have shown to improve a broad range of outcomes, the authors note a lack of accessibility to such interventions in mental health settings. Furthermore, intervention studies targeting stress reduction in psychosis often lack a proper assessment of stress and HPA axis function.

A recently developed program for high school children has proven effective in averting high stress levels and elevated cortisol levels and thus prevent the onset of mental illness. In her de-stress for success program, Lupien and colleagues developed a school based education program to alleviate the stress of transition to high school. The authors observed that students whose cortisol levels decreased in response to the intervention also had a significantly decreased risk for depressive symptomatology three months post intervention (Lupien *et al.*, 2013). Specifically designed stress management programs for psychosis have furthermore shown a reduction in hospital admission in the year following the intervention (Norman *et al.*, 2002). There is a critical need for further intervention studies investigating the effectiveness of

alternative pharmacological and psychosocial interventions to alleviate subjective and physiological stress response, with the ultimate goal to reduce the risk for psychosis onset and progression. Here, knowledge about inter-individual differences in stress vulnerability and psychosis risk can lead to the development of targeted interventions and assessment of their effectiveness.

11.6 Conclusions

In conclusion, the present paper provides a thorough review of the recent evidence on HPA axis dysregulation among individuals with and at-risk for psychotic disorders, taking into consideration how abnormalities within the HPA axis might interact with other neurobiological systems to give rise to psychosis. Based on the complexity of these findings, we have proposed an extension of the original neural diathesis stress model, and have provided suggestions for further research in the field. We hope that this review sensitizes researchers towards the multiple methodological challenges that can obscure the interpretation of findings and stimulates the design of guidelines for investigation of HPA axis activity in the context of psychosis. This is expected to ultimately advance our understanding of stress and stress-system related mechanisms for the etiology of psychotic disorders and may help to identify successful treatments to prevent psychosis onset and progression of symptoms.

Figure Captions

Table 1: Summary of cortisol abnormalities among individuals with established psychosis and at-risk groups relative to healthy controls. Upward arrow indicates increased cortisol in patient/high-risk group relative to healthy controls; Downward arrow indicates decreased cortisol levels in patient/high-risk group relative to healthy controls; – no difference between patient/high-risk group and healthy controls; 2-DG: 2-deoxy-D-glucose.

Figure 1. The extended neural diathesis-stress model of schizophrenia: (A) Rightward arrows indicate the contribution of vulnerability factors to neurodevelopmental alterations that predispose the individual to maladaptive responses to later stressors, eventually increasing the risk for psychosis onset. Leftward arrows from psychosis progression illustrate the potential for prodromal/psychotic symptoms to both aggravate the cascade of neurobiological disturbances and further enhance vulnerability. (B) Downwards arrows indicate the progression of psychosis from early antecedents to chronic illness. (C) Curved arrows depict the bidirectional cause and effect relationship between HPA axis alterations and degenerative brain processes. (D) Two-way arrows emphasize the complex interactions between the HPA axis and other biological systems. (E) Dashed arrows demonstrate the downstream effects of brain degenerative processes. HPA: hypothalamus-pituitary-adrenal axis; CHR: clinical high risk.

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